ABSORBED DOSE ESTIMATION AND PREDICTION OF IRRADIATION EFFECTS IN RADIONUCLIDE THERAPY EXPERIMENTS WITH MICE MODEL

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ABSTRACT
As the sizes of mouse organ are comparable with the range of the high-energy beta particles emitted by the radionuclides commonly used in radionuclide therapy (RNT) a significant amount of beta radiation emitted could be imparted to the adjacent tissues. The often assumption that beta particles are full-absorbed in the emission site is then not satisfied. The MIRD’s formulation was adapted to perform absorbed dose calculation for $^{131}$I, $^{90}$Y and $^{177}$Lu by using absorbed fraction for mice previously reported. Two approaches were considered: a) cross irradiation due to the high-energy beta particles emitted in the neighborhood of organ target and b) self-irradiation when the beta particles are considered full-absorbed in the emission site. Calculations with a modified formulation of linear-quadratic model to be used in the RNT were done for prediction of radiation effects on tumor, bone marrow (BM) and kidneys. The influence of cross irradiation condition was diverse for the tissues analyzed here. The absorbed dose values in kidneys calculated for both methods were no significantly different for low energies, but variations around to 40-50% (over- or under-estimation) in absorbed dose were obtained for high energies. Approximately a 30% of the beta radiation emitted from bone will cross-irradiates the BM. For injected activities values higher than 10MBq (300µCi) the absorbed dose in BM exceeds the tolerable limits (2Gy). The formulation presented here could be used in the design of refined experiments for RNT with mice model where the radio-myelotoxicity needs to controlled.

Key words: absorbed dose, mice model, radionuclide therapy, beta emitters, LQ model.

1. INTRODUCTION
The size of mouse organ are comparable with the range of the high-energy beta particles emitted by the radionuclides commonly used un radionuclide therapy (RNT). It can results in a significant amount of the beta radiation emitted in a tissue could be imparted to the adjacent tissues. Therefore, the often used MIRD’s assumption of non-penetrating radiation is fully absorbed in the emission site or source tissue is not adequate when organ absorbed dose calculation will be done using a mouse model. The results of calculation performed by Hui et al [1] and Miller et al [2] predicts that even for larger organs like liver, more than 30% of beta energy emitted escapes from the source organ. Consequently a separate dosimetry model should to be considered if a more accurate interpretation of any radiotoxic observed event is being desired.

Two different approximations for the calculation of dose conversion factor to be used in animal model had been reported in the literature. The first is based on geometrical approximated shape organ [1],[3] sometimes is called as stylized model. In the second approach voxel dosimetry techniques had been used [4]-[6]. Either point-kernel or Monte Carlo codes had been used for the cases above mentioned. Although it seems lesser exact, the stylized models are more practical in use and there is a good agreement between the results obtained by using these methods for the self- and cross-absorbed fraction for high-energy beta emitters. Otherwise the differences in the worse case are similar to those found with typical biodistribution data.

Bone marrow (BM) is the main dose-limiting organ in RNT applications. Further toxicity in spleen and kidneys had been reported [7]. Therefore the BM and kidneys responses to irradiation should be addressed if hemotoxicity reaction and renal failures wants to be predicted or avoided in the best case. The estimation of absorbed dose in BM become difficult because it is no easy a direct measurement of activity in this tissue [8]-[12].

In this work the MIRD’s formulation for internal dose calculation in tissue was adapted in order to more realistic absorbed dose calculation in mice considering cross-irradiation because high-energy beta particles could be done. A modified formulation of linear-quadratic model to be used in the RNT previously reported by González et al [13] was used for the prediction of radiation effects on tumor, bone marrow (BM) and kidneys which was.
2. METHODOLOGY

The absorbed dose calculation in mice were done under the MIRD’s formulation, but considering a fraction of beta radiation could escape from the emission site to the neighbor tissues (cross-irradiation condition). The results were compared with the often used assumption that non-penetrating radiation will be full-absorbed into the source organ (self-irradiation condition).

As the MIRD’s scheme had stated [13],[14] the total mean absorbed dose in a k-target organ $D_k$ [Gy] from the activity cumulated in N source organs is calculated in general by

$$D_k = \frac{1}{m_k} \sum_k \bar{A}_k \sum_i \left[ \Delta_{\text{np},i} \phi_{\text{np},i}(k \leftarrow h) + \Delta_{\text{p},i} \phi_{\text{p},i}(k \leftarrow h) \right]$$

(1)

where:

- $m_k$: target-organ mass,
- $\bar{A}_k$: cumulated activity in the h-th source organ,
- $\Delta_{\text{np},i}$: total energy emitted per disintegration for the i-th non-penetrating emitted radiation,
- $\phi_{\text{np},i}(k \leftarrow h)$: absorbed fraction in the k-target organ of the energy emitted in the h-source organ,
- $\Delta_{\text{p},i}$: total energy emitted per disintegration for the i-th penetrating emitted radiation
- $\phi_{\text{p},i}(k \leftarrow h)$: absorbed fraction in the k-target organ of the energy emitted in the h-source organ.

The equation (1) can be divided in two dose-contributors terms: the absorbed dose because of the energy self-absorbed into the target or $D_{\text{self},k}$ and the absorbed dose from the energy cross-emitted by the h-source organs or $D_{\text{cross},k}$, therefore the absorbed dose in a k-target organ can be represented as:

$$D_k = D_{\text{self},k} + D_{\text{cross},k}$$

(2.1)

where

$$D_{\text{self},k} = \frac{1}{m_k} \bar{A}_k \sum_i \left[ \Delta_{\text{np},i} \phi_{\text{np},i}(k \leftarrow k) + \Delta_{\text{p},i} \phi_{\text{p},i}(k \leftarrow k) \right]$$

(2.2)

$$D_{\text{cross},k} = \frac{1}{m_k} \sum_{(h \neq k)} \bar{A}_h \sum_i \left[ \Delta_{\text{np},i} \phi_{\text{np},i}(k \leftarrow h) + \Delta_{\text{p},i} \phi_{\text{p},i}(k \leftarrow h) \right]$$

(2.3)

The contribution of penetrating radiation to total dose is considered very small, then $\phi_{\text{p},i}(k \leftarrow k) = \phi_{\text{p},i}(k \leftarrow h) \approx 0$. The cross-irradiation condition considers that only high energy beta particles emitted will be able to produce cross-irradiation to close-neighbors tissues and the other one will be full-absorbed in the origin site, that means: $\phi_{\text{np},i}(k \leftarrow h) = 0$; $\phi_{\text{np},i}(k \leftarrow k) = 1$. The self-irradiation condition could be imposed in equations (2.2)-(2.3) by making $\phi_{\text{p},i}(k \leftarrow h) = 0$ and $\phi_{\text{p},i}(k \leftarrow k) = 1$. During the clinical practice or research it is often to use the total number of decays per MBq of injected activity $r_i = \bar{A}_i / A_{\text{inj}}$ instead $A_i$, where $A_{\text{inj}}$ is the injected activity. In that case the absorbed dose value calculated by the equations (2.2) and (2.3) will be expressed in Gy/MBq of injected activity. All the self- and cross-absorbed fractions for beta particles used in our calculation were those calculated by Hui et al [1] and Miller et al [2].

The calculations for the prediction of irradiation effects in tumor, BM and kidneys were performed by using the framework established by the LQ model for irradiation at low dose rate (LDR). The biological equivalent dose (BED) was calculated as it was proposed by González et al [13] where dose rate is described as a multi-exponential time-dependant functions and cell proliferation contribution was considered. For the description of the irradiation effects using the LQ model the dose rate function that rule out the irradiation scheme should be found. Analogous expressions could be obtained for the calculation of dose rate [Gy/hours] following a similar thinking path that we followed before to obtain the equations (2.1)-(2.3):

$$r_k(t) = r_{\text{self},k}(t) + r_{\text{cross},k}(t)$$

(3.1)

where:

$$r_{\text{self},k}(t) = \frac{1}{m_k} \bar{A}_k \left[ \Delta_{\text{p},k} \phi_k(k \leftarrow k) + \sum_{i \neq \beta} \Delta_{\text{np},i,j} \right]$$

(3.2)

$$r_{\text{cross},k}(t) = \frac{\Delta_{\text{p}}}{m_k} \sum_{(h \neq k)} A_h(t) \phi_{\text{p},h}(k \leftarrow h)$$

(3.3)

where:

- $A(t)$: uptake-elimination activity profile

It should be noted that the cross-irradiation condition was imposed in the expressions. As during the clinical practice or research it is common to use the fraction of injected activity ($A_{\text{inj}}$) profiles $FIA_i(t) = A_i(t)/A_{\text{inj}}$ instead $A_i(t)$ profile the equation (4.2)-(4.3) should be normalized by $A_{\text{inj}}$ and the dose rate calculated by the equations (4.2)-(4.3) will be expressed in Gy/hour/MBq injected activity units. The simulated $FIA_i(t)$ profiles for the k-th organ were fitted to a sum of two exponential. The bioinformatics data (retention fractions and effective times) were simulated from typical bioinformatics data often reported for mice models.

The absorbed fractions for $^{131}I$, $^{90}Y$ and $^{177}Lu$ were those reported by Flynn at al [4] and Miller et al [2]. The tissues masses used during the whole body dose estimation were those reported by Miller et al in [2]. The equilibrium constant for beta particles and other non-penetrating
radiation emitted by these radionuclides were calculated using the energies and yields reported at the RADAR’s website [http://www.doseinfo-radar.org]. Table I shows the LQ parameters used during the calculation.

### Table I
Parameters for LQ model. The values into brackets are the papers from where the values were taken.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiosensitivity, $\alpha$, Gy$^{-1}$</td>
<td>0.3</td>
</tr>
<tr>
<td>LQ radiosensitivity, $\alpha/\beta$, Gy</td>
<td>10$^{[15]}$</td>
</tr>
<tr>
<td>Doubling time, $T_D$, days</td>
<td>7</td>
</tr>
<tr>
<td>Mean repair time, $T_{rep}$, hrs</td>
<td>1.5</td>
</tr>
</tbody>
</table>

3. RESULTS

The figure 1 shows the simulated dose rate profiles calculated for kidneys, BM and bone for the cross-irradiation condition as it was established in the equations (3.1)-(3.3). The BM profile was estimated by considering the activity concentration in BM equals to 0.36 times the activity concentration in blood, like it was assumed by Muthuswamy et al$^{[14]}$.

The effect of the dosimetry condition (self-irradiation or cross-irradiation) on the estimation of the dose rate function is showed in the figure 2 (upper panel). For lower energy ($^{131}$I), no differences in dose rate and absorbed dose estimation were found for bigger tissues, like liver or kidneys for both condition. As energy is increased the differences in the dose estimation becoming critical even for bigger tissues and even more for bone, BM or spleen. The relative differences for the extrapolated initial dose rate were around of 40-50% for $^{90}$Y.

As it is showed in the figure 2 (lower panel), for high energy the dose rate and the absorbed dose trends to be under-estimated for smaller tissues when self-irradiation is considered in the calculations. The absorbed dose is the area under the curve in the dose rate profile. Conversely the absorbed dose for high energy particles is over-estimated for bigger tissues for this condition, see figure 2 (upper panel).

For the calculation of BED using the LQ model $^{[13]}$ the dose rate profiles obtained for cross-irradiation condition were fitted to a bi-exponential function. The calculation were done for kidneys, BM and tumor and using the radiobiological parameter given in the table I. The injected activity was ranged between 3.7- 11MBq (100-300µCi) as activities values often used in RNT studies with experimental animals. The results shows that more than 10MBq produces absorbed dose in BM higher that tolerable limits of 2Gy. Nevertheless, the injection of low activity to avoid the myelosupression will produce a lost in the effectiveness of treatment on tumors, but schemes will multiple administration could be an option to overcome this situation.

4. DISCUSSION

Kidneys and BM are commonly considered as critical tissues during clinical or experimental applications of RNT. It should be noted that absorbed dose calculation must be
performed with the correct assumption to avoid the irradiation side-effects.

The magnitude of the differences on the calculations was different for all organs simulated and it is dependent of organ sizes and the energy of beta particles. For high energy, the dose rate and the absorbed dose trends to be under-estimated for smaller tissues when self-irradiation is considered in the calculations. Conversely the absorbed dose is over-estimated for bigger tissues for this condition for high energy particles.

From the anatomical differences between mouse and human results that the hypothesizes often used for human patient during dose calculation should be carefully evaluated when MIRD scheme will be applied for dose calculation in mouse model. The size of mouse organ are comparable with the range of the high-energy beta particles therefore the assumption of total absorption of non-penetrating radiation in the origin tissue is not fulfilled. In consequence the fraction of beta radiation which is imparted in the surrounding tissues must be taken into account during the dose calculation with mice data [1]-[3],[5].

The influence of cross-irradiation condition was diverse for the measured organs. For the critical organs considered here, the absorbed dose values in kidneys were no significantly different for low energy, but a variation around 50% in absorbed dose (relative difference) was obtained in bone and kidneys for high energies. Approximately more that 50% of the beta radiation will cross-irradiates the bone marrow and near to 20% of radiation emitted from marrow will cross-irradiated to bone. It should be the cause of the differences in the absorbed dose calculation for bone and marrow. This detail is not predicted when self-irradiation is assumed in the absorbed calculation. On the other hand, the photon contribution was not considered since its contribution to the absorbed dose per disintegration could be near of 5% [5], but it must be taken into account in the adequate cases if more accurate calculation are desired. This issue must be carefully evaluated and more calculation of dose conversion factor for mouse dosimetry model should be made.

Since the radioactivity in BM was not directly measured an estimation was done by considering that a fraction of activity measured in blood could be used as a representation of uptake in marrow. An interesting results is that cross-contribution increase the irradiation effective time in BM. It is not predicted when self-irradiation is assumed. Nevertheless, direct measurement of the activity in BM biopsies will give us the best approximation for the estimation of absorbed dose.

The results shows that more than 10MBq (300µCi) produces absorbed dose in BM higher that tolerable limits of 2Gy. Some studies had been showed that myelotoxicity is observed in mice for injected activities higher than 7.4MBq with radiopharmaceutical labeled with 188Re [17],[18].

5. CONCLUSIONS

The formulation presented here could be used to design therapeutic experiments with mice model using beta emitter radionuclides. Further works should be done to acquire more data of absorbed dose in mice organ that could be used for better dose estimation. These findings let us the integration of dose calculation in radiobiological model for prediction of treatment response when beta particles with high energy are used in these models.

REFERENCIAS


