1st International Workshop on Space Radiation Research and
11th Annual NASA Space Radiation Health Investigators' Workshop
Arona (Italy), May 27-31, 2000

Inactivation of individual cells by divers ions at different LET values

M.V. Lokajíček, T. Čechák, L. Judas, J. Klusoň, V. Kundrát, K.Prokeš

Institute of Physics, Academy of Sciences, Prague (Czech Republic)
Department of Dosimetry, Czech Technical University, Prague (Czech Republic)
Department of Oncology, Charles University, Prague (Czech Republic)

Abstract

A new formula linking the shape of survival curve to the inactivation probabilities after different numbers of cell hits has been derived. It has been used in analyzing recent experimental data obtained with monolayer cells irradiated at definite values of LET (in different parts of Bragg peaks). The new approach allows not only deriving the values of inactivation probabilities at given LET values; unexpected consequences seem to follow especially for inactivation characteristics of carbon ions in different parts of the Bragg peak, too.

KEYWORDS: Survival curves, cell inactivation, LET dependence.

1. Introduction

The effective application of different ions in tumour radiotherapy as well as the safety of astronauts require improved understanding of the basic characteristics of radiobiological mechanism in individual cells. An important progress in this direction has been enabled by experiments in which a whole population of cells have been hit by ions at defined average values of LET (irradiation of cells in a monolayer by different parts of Bragg peaks) and the corresponding survival curves have been established.

In the following some new results obtained by a detailed model analysis of such experiments will be presented. Such a model analysis has been enabled when a close relation of the shape of survival curves to cell inactivation probabilities at different hit numbers has been found.

2. Inactivation probability and the shape of survival curves

Inactivation probabilities of individual cells in dependence on the LET value may be derived from the corresponding survival curves. If λ [keV/μm] is a given LET value one can write for the average number of cell hits at a dose D

$$h_D = hD, \qquad h = \overline{C}s/\lambda$$

where s [μm^2] is the cross section of cell nucleus (or of chromosome system) and $\overline{C}$ = 6,24 [keV/μm].

The survival curve at a given λ may be then expressed as

$$s_\lambda(D) = 1 - \sum_{k=1}^{\infty} P_k p_k^{(\lambda)}, \qquad P_k = h_D^k e^{-h_D}/k!$$

where $p_k^{(\lambda)}$ represents the inactivation probability when a cell nucleus is hit k times, the corresponding probability being given by P_k. It holds

$$\sum_{k=0}^{\infty} P_k = 1, \qquad 0 = p_0 \le p_k \le p_{k+1} \le 1.$$

It is then possible to write further

$$\sigma_\lambda(D) = -\lg s_\lambda(D) = \Sigma_k \alpha_k^{(\lambda)} D^k \tag{1}$$

where

$$\alpha_1^{(\lambda)} = hp_1,$$

$$\alpha_2^{(\lambda)} = \frac{h^2}{2}\left[(1-p_1)^2 - (1-p_2)\right],$$

$$\alpha_3^{(\lambda)} = \frac{h^3}{6}\left[-2(1-p_1)^2 + 3(1-p_1)(1-p_2) - (1-p_3)\right],$$

and similarly for higher terms of the corresponding Taylor series; all p_k being λ-dependent, too. It means that the survival curve (1) may be parameterized with the help of inactivation probabilities p_k after given numbers of cell hits.

If the inactivation probability p_k increased on the mere geometrical principle, i.e.,

$$p_k^{(\lambda)} = 1 - \left(1 - p_1^{(\lambda)}\right)^k,$$

one should obtain

$$\sigma_\lambda(D) = hp_1^{(\lambda)} D$$

and the survival curve would be represented by a straight line in the semilogarithmic graph. In a general case it is possible to write, e.g.

$$p_k^{(\lambda)} = 1 - \left(1 - p_1^{(\lambda)}\right) e^{-k\omega p_1^{(\lambda)}} / e^{-\omega p(\lambda)} \qquad (2)$$

where ω may depend on λ as well as on the kind of applied ions.

3. Numerical analysis of survival curves for protons

It is evident that the free parameters $\alpha_k^{(\lambda)}$ and s may be derived from the experimental data for diverse values of λ if the corresponding survival curves had been established. Using Eq. (2) and putting, e.g.

$$\omega = \omega_0 + \omega_1 \bar{\lambda} + \omega_2 \bar{\lambda}^2$$

where $\bar{\lambda} = \log \lambda$ the number of free parameters may be reduced significantly. The remaining free parameters are then $p_1^{(\lambda)}$, s, and ω_j (j = 0,1,2); their total number being practically always lower than the number of experimental points in data being available.

We have analyzed the experimental data from two different experiments published recently for protons (see Refs. [1] and [2]). Our orientation fit has led in the first case [1] to the following values:

$s = 25 \mu\text{m}^2$; $\omega_0 = 0.84$, $\omega_1 = 0.2$, $\omega_2 = -0.05$;

and to the values of $p_1^{(\lambda)}$ up to $k = 5$ for individual values of λ:

λ [*keV/*μ*m*	h	p_1	p_2	p_3	p_4	p_5
11	14.5	.030	.059	.087	.114	.140
20	8.0	.072	.137	.198	.253	.303
31	5.1	.143	.245	.332	.413	.493
64	2.5	.218	.360	.459	.531	.583
80	1.8	.281	.401	.552	.605	.664

In the other case [2] we have obtained:

$s = 15\ \mu\text{m}^2$; $\omega_0 = 0.90$, $\omega_1 = 0.2$, $\omega_2 \approx 0.$;

λ[*keV/*μ*m*]	h	p_1	p_2	p_3	p_4	p_5
10	9.8	.064	.122	.173	.218	.259
18	5.4	.069	.130	.190	.251	.316
28	3.5	.171	.324	.459	.574	.671

The values of free parameters differ slightly in individual cases, which may follow from different irradiation arrangements.

Similar analyses have been performed for deuterons and helium ions, too; data taken from refs. [2, 3]. The results obtained will be presented elsewhere [5].

4. Analysis of experimental data for carbon ions

It is commonly believed that in the Bragg peak of carbon ions (at least at higher values of λ) already the values of $p_1^{(\lambda)}$ are practically equal to one. However, the experimental data being available for these ions do not seem to support such an assumption. That the situation may be different follows from the recently published data [4] that have concerned isoeffective irradiation of the mouse skin under divers conditions: different numbers of dose fractions and different values of λ. As mentioned already by the authors of ref. [4] one should ask why, e.g. the curve for $\lambda = 100$ *keV/*μ*m* differs so significantly from the curves obtained for $\lambda = 10$*-50 keV/*μ*m* and resembles rather the behavior obtained for X rays.

The irradiation conditions are very similar to the preceding monolayer experiments as a narrow layer of clonogenic cells may be regarded as responsible for macroscopic skin effect. Assuming: (i) the macroscopic effect is given by the survival $S_\lambda(D_{N,\lambda}, N)$ of clonogenic cells under corresponding conditions; (ii) no cell proliferation occurred during the irradiation course (total time *T < 10 days*), it should hold

$$S_\lambda(D_{N,\lambda}, N) = \exp(-C_\lambda(D_{N,\lambda}, N)),$$
$$C_\lambda(D_{N,\lambda}, N) = N\sigma_\lambda(D_{N,\lambda}/N)$$

where $D_{N,\lambda}$ is the corresponding total dose and N – the number of fraction doses used.

The given skin effect (moist desquamation) may be then characterized by the common quantity C and it must hold for all experimental points (shown in ref. [4])

$$C_\lambda(D_{N,\lambda}, N) = C.$$

Using the same parameterization for $\sigma_\lambda(d)$ as in the previous case the following free parameters would now be available: $p_1^{(\lambda)}$, s, C, ω_j (j = 1,3). However, it was not possible to obtain an acceptable fit under such conditions.

An agreement with available experimental data could be obtained only if the parameter s has been substituted by a function of λ:

$$s_\lambda = s_0(1 + \alpha_1\lambda + \alpha_2\lambda^2).$$

The following values of free parameters have been then obtained. The macroscopic effect may be characterized by *C=8.06* which corresponds to the survival cell ratio of *0.0003.* And further,

$$s_0 = 0.48\ \mu m^2, \quad a_1 = 0.253, \quad a_2 = 0.0076;$$
$$\omega_0 = 1.07, \quad \omega_1 = -1.38, \quad \omega_2 = 0.84\ .$$

The values of corresponding p_k^λ are shown in the following table:

λ [*keV/μm*]	s_λ [μm²]	h	p_1	p_2	p_3	p_4	p_5
14	1.4	0.61	.412	.432	.625	.631	.905
20	2.1	0.64	.378	.537	.656	.733	.798
40	5.3	0.82	.325	.499	.620	.709	.780
50	7.4	0.92	.275	.413	.575	.711	.837
60	9.8	1.02	.229	.361	.555	.739	.901
80	15.8	1.23	.217	.378	.541	.696	.826
100	23.1	1.44	.161	.272	.435	.625	.816

It is necessary to conclude that the energy transferred by individual carbon ions to individual cell nuclei is much smaller than it has been commonly expected at the given λ values. However, a greater number of cells might be hit by one ion in a layer perpendicular to the original beam direction.

5. Conclusion

The proposed mathematical model linking the shape of survival curve to the inactivation probabilities of cells after different numbers of hits opens a new way of studying the processes running in a cell after radiation impact. Our analysis shows also convincingly how misleading may be the application of the simple LQ model when trying to understand the radiobiological mechanism in cells.

As to the carbon ions it is evident from the experimental data and their analysis that the effect on cells at higher λ differs significantly from that commonly expected. The analysis performed by us indicate that the hitherto philosophy the application of carbon ions in radiotherapy has been based on should be rather fundamentally revised. On the other side, the approach of evaluating the values of λ at different parts of Bragg peaks should be reexamined, too.

Acknowledgements

Work supported by Grant Agency of the Czech Republic, project No. 202/99/1115.

REFERENCES

[1] Belli M et al. Inactivation and mutation induction in V79 cells by low energy protons; reevaluation of the results at the LNL facility. Int J Radiat Biol 1993: 63; 331-337.
[2] Folkard M et al. Inactivation of V79 cells by low-energy protons, deuterons and helium-3 ions. Int J Rad Biol 1996: 69; 729-738.
[3] Belli M et al. Inactivation induced by deuterons of various LET in V79 cells. Radiat Prot Dosimetry 1994: 52; 305-310.
[4] Ando K et al. Mouse skin damages caused by fractionated irradiation with carbon ions. 6th Workshop on Heavy Charged Particles in Biology and Medicine. Baveno (Italy), September 28-October 1, 1997. GSI Report 97-09, edited by Kraft G and Langbein K (GSI, Darmstadt).
[5] Judas L, Lokajíček MV. Cell inactivation by ionising particles and the shapes of survival curves (submitted to J Theor Biol).