

CONF-960929--1

RECEIVED
OCT 22 1996

AN HSEF FOR MURINE MYELOID LEUKEMIA

*V.P. Bond, *E.P. Cronkite, *J.E. Bullis, *C.S. Wu, *S.A.
Marino and *M. Zaider*Brookhaven National Laboratory, Upton, NY 1173, and
*Department of Radiation Oncology, Columbia University, New
York, NY 10032, USA

OSTI

I. Introduction

In the past decade, a large amount of effort has gone into the development of hit size effectiveness functions (HSEFs), with the ultimate aim of replacing the present absorbed dose-RBE-Q system¹⁻³. The reasoning has been that, while cancers of course are observable only at the organ-organism level of biological organization, they are in fact single-cell in origin, i.e. an observed malignancy is no more than a marker for a fully-transformed cell constituting an incipient cancer. However, the absorbed dose determined at the tissue level is incapable of providing information on single hits on (doses to) the single cell. As a result, it is necessary to resort to microdosimetry, which is capable of providing not only the number of hits on cells, but the distribution of hit sizes as well. From this information, an HSEF can be derived.

However, to date there have been no sets of data available on animals exposed to radiations of several qualities, and for which microdosimetric data were available. Thus, it was possible to obtain HSEFs only for endpoints observable in the single cell, e.g. mutations or chromosome abnormalities of various types, which were thought to have some relevance to the carcinogenesis process.

The objective of the present set of experiments was to remedy this situation. Large numbers of mice were exposed to radiations of several different qualities, and were observed throughout their entire lifespan for the appearance of myeloid leukemia. The HSEF developed for this neoplasm is presented and discussed.

II. Materials and Methods

Animals: All studies were performed on 12-16 week old male CBA/CaJ mice, either purchased from the Jackson Laboratory or bred at the Brookhaven National Laboratory (BNL). The mice were maintained at BNL in AAALAC-approved quarters, on a twelve-hour light/dark cycle, and given acidified drinking water (pH 2.4) and Purina Lab Chow ad libitum.

Exposures: Photon exposures were to both X rays and ¹³⁷Cs. All animals were irradiated at 84 days of age. X-ray exposures were done in the BNL Medical Department, using 250 kVp x rays

DISTRIBUTION OF THIS DOCUMENT IS UNLIMITED

MASTER

DISCLAIMER

This report was prepared as an account of work sponsored by an agency of the United States Government. Neither the United States Government nor any agency thereof, nor any of their employees, makes any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any specific commercial product, process, or service by trade name, trademark, manufacturer, or otherwise does not necessarily constitute or imply its endorsement, recommendation, or favoring by the United States Government or any agency thereof. The views and opinions of authors expressed herein do not necessarily state or reflect those of the United States Government or any agency thereof.

DISCLAIMER

Portions of this document may be illegible in electronic image products. Images are produced from the best available original document.

with 0.5 mm Cu + 1.0 mm Al filtration and a dose rate of 30 cGy/min. Gamma ray exposures were done at BNL using a dose rate of approximately 50 cGy/min.

All neutron exposures were done at the Radiological Research Accelerator Facility (RARAF), a Van de Graaff machine located at the Irvington Nevis Laboratories of Columbia University. The device produces essentially monoenergetic neutrons of various mean energies. Those selected were: 0.22; 0.44; 1.5; 6.0; and 14.0 MeV. Dose rates ranged from 5 to 60 cGy/hr.

All animals were checked twice daily, seven days per week. Those that appeared to be ill or moribund were euthanized. The body cavities were opened and the remains were placed in 10% formalin. Samples of the sternum, spleen, lymph nodes, thymus, lungs, liver, and kidney were taken. Tissues were stained with hematoxylin and eosin. One of the authors (EPC) was responsible for evaluation of the histological findings.

III. Results and data analysis

The results of these experiments consist of $K=7$ data sets, each set corresponding to a particular radiation type. Within each set, k , irradiations have been performed at $J(k)$ different doses. Following exposure to dose D_{kj} , animals are observed for I consecutive time intervals, Δt , and for each interval, i , one records the number of animals, N_{kji} , that died during that time period and among these, the number of animals, M_{kji} , that have a tumor.

To analyze the data we adopt the relative risk model (also known as the proportional-hazard model) in which the cancer hazard rate, $\lambda(t,D)$, at time t after exposure to dose D is factorized into dose-dependent and time-dependent terms:

$$\lambda(t,D) = \eta(D) \cdot \lambda_0(t) \quad (1)$$

The main reason for using this expression is the ability to retain the concept of a time-independent "dose response function". The hazard rate, $\lambda(t,D)\Delta t$, is the probability of observing a malignancy in time interval Δt among all the animals that were cancer-free at the beginning of the interval. The quantity obtainable from experiment, however, is the cumulative cancer rate, $F(t,D)$, which is the probability that an animal has a malignancy at time t . The two functions are equivalent to each other via:

$$F(t,D) = 1 - \exp\left[-\int_0^t \lambda(t',D) dt'\right], \quad (2)$$

as can be easily verified. From Eqs(1,2) one obtains:

$$F(t,D) = 1 - [1 - F_0(t)]^{\eta(D)}, \quad (3)$$

where $F_0(t) = F(t,0)$. We further express $\eta(D)$ as a linear quadratic function of dose:

$$\eta(D) = 1 + \alpha D + \beta D^2. \quad (4)$$

Note that α and β depend only on the radiation type (k) while $F_0(t)$ depends only on the time (i). We shall treat $F_0(t)$ non-parametrically, that is assume no particular functional form for this quantity. The unknowns of the problem are then α_k , β_k , and $F_{0,i}$ with $k=1,2,\dots,K$; $i=1,2,\dots,I$.

Estimators for these parameters may be obtained in the maximum likelihood sense. The log-likelihood function for this problem is⁴:

$$\log L = \sum_{k=1}^K \sum_{j=1}^{J(k)} \sum_{i=1}^I \{M_{kji} \log[1 - (1 - F_{0,i})^{\eta_{kj}}] + (N_{kji} - M_{kji}) \eta_{kj} \log[1 - F_{0,i}]\} \quad (5)$$

subject to a) positivity constraints on all the unknowns, and b) the requirement that $F_0(t)$ is a monotonically non-decreasing function of t .

Fig.1 shows an example of the solution $F(t,D)$ for one of the five neutron energies used in this study (1.5 MeV, solid lines). Also shown (circles) is the fraction of animals with malignancies in each time interval. For this analysis we have used $\Delta t = 50$ days. Note that the solid line is **not** meant to be a fit to the data. The α and β values thus obtained are given in Table 1.

IV. Hit-size effectiveness function

A main goal of this study has been to obtain information on the effectiveness of single microdosimetric events (hits) to induce the alterations that lead to murine leukemia. This is formalized in the equation:

$$\epsilon(D) = \int_0^{\infty} h(z) f(z;D) dz. \quad (6)$$

Here $f(z;D)$ is the (multi-event) microdosimetric spectrum at dose D and $h(z)$ is the hit-size effectiveness function assumed to depend on specific energy, z , only. It can be shown² that at low dose - where, on average, there is less than one event per cell - Eq(6) reduces to:

$$\epsilon(D) \approx D \int_0^{\infty} \frac{h(z)}{z_F} f_1(z) dz. \quad (7)$$

In this expression $f_1(z)$ is the single-event microdosimetric spectrum and z_F is its first moment. By comparing this expression with Eq(4) one obtains:

$$\alpha = \int_0^{\infty} \frac{h(z)}{z_F} f_1(z) dz = \int_0^{\infty} q(z) d(z) dz \quad (8)$$

$q(z)$, which equals $h(z)/z$, has been termed specific quality factor² and it has the same conceptual meaning as $h(z)$, except

that it refers to the dose distribution in specific energy, $d(z)$, and it is thus closer to the conventional definition of quality factor in health physics.

Eq(8) can be used to obtain information on $q(z)$ or $h(z)$ as follows: in a series of experiments (such as those reported here), the initial slopes of the dose effect curves (α_i) as well as microdosimetric distributions, $d_i(z)$ are measured for a series of radiations, i . The integral equation, Eq(8), can be then converted to a system of integral equations and solved numerically².

In this analysis the α values have been converted to RBE (see the last column of Table 1), i.e. normalized to the value obtained for ¹³⁷Cs gamma rays.

Microdosimetric spectra for the radiations used in this study have been calculated as follows: For photons let $N(E_\gamma)$ denote the photon energy spectrum and let $f(y, E_\gamma)$ represent the single-event microdosimetric distribution in lineal energy that results from exposure to monoenergetic photons of energy E_γ . The microdosimetric spectrum for the entire photon field is given by:

$$f(y) = \int_0^{\infty} \frac{N(E_\gamma) E_\gamma \mu(E_\gamma)}{y_F(E_\gamma)} f(y, E_\gamma) dE_\gamma / \int_0^{\infty} \frac{N(E_\gamma) E_\gamma \mu(E_\gamma)}{y_F(E_\gamma)} dE_\gamma \quad (9)$$

Here y_F is the frequency-averaged lineal energy and μ is the linear attenuation coefficient. Microdosimetric spectra for monoenergetic photons, $f(y, E_\gamma)$, are calculated with the following equation:

$$f(y, E_\gamma) = \int_0^{\infty} \frac{n(E_\gamma, E_e) E_e}{y_F(E_e)} f(y, E_e) dE_e / \int_0^{\infty} \frac{n(E_\gamma, E_e) E_e}{y_F(E_e)} dE_e \quad (10)$$

Here $n(E_\gamma, E_e)$ is the energy spectrum of electrons generated by photons of energy E_γ ; and $f(y, E_e)$ is the microdosimetric spectrum of electrons of energy E_e . The distribution $n(E_\gamma, E_e)$ has been obtained using the computer code PHOEL⁵. Microdosimetric spectra for monoenergetic electrons were calculated using our own event-by-event transport codes⁶.

Microdosimetric spectra for neutrons have been calculated using the concepts of crossers, stoppers, insiders and starters introduced by Caswell⁷. A detailed description of our code can be found in Ref.8. This approach has been shown to reproduce quite accurately the experimental spectra.

The function $q(y)$ obtained in this analysis is shown in Fig.2; also shown here is the HSEF function $h(z)$. They have been obtained by applying the Bayes theorem and maximum entropy principle⁹ to the problem of solving Eq(8).

V. Conclusion

The accuracy possible in this analysis was limited because the population used was mice, with each observed leukemia

representing but one cell that has been fully transformed malignantly. The sigmoid shape of the obtained function is reassuring and indicates that the HSEF - with complementary data - can be used to develop an internally consistent and coherent system for use in radiation protection practice.

Table 1

	α / Gy ⁻¹	β / Gy ⁻²	RBE
250 kVp x rays	0.12	0.	2.4
¹³⁷ Cs	0.050	2.6 10 ⁻⁴	1
220-keV n	0.88	0.	17.8
440-keV n	0.39	1.7 10 ⁻³	7.8
1.5-MeV n	0.43	0.	8.6
6-MeV n	0.16	0.	3.2
14-MeV n	0.12	0.	2.4

LITERATURE CITED

1. V.P. Bond and M.N. Varma, Proceedings of the Eight Symposium on Microdosimetry. London: Harwood Academic, pp. 423-437 (1982).
2. M. Zaider, and D.J. Brenner, Radiation Research 103: 302-316 (1985).
3. C.A. Sondhaus, V.P. Bond, and L.E. Feinendegen, Health Phys. 59: 35-48 (1990).
4. D. Chmelevsky, A.M. Kellerer, J. Lafuma, and J. Chameaud, Radiat. Res. 91: 589-614 (1982).
5. J.E. Turner, R.N. Hamm, H.A. Wright, J.T. Modolo, and G.M.A.A. Sardi, Health Phys 39: 49-55 (1980).
6. M. Zaider, A.Y.C. Fung, and M. Bardash, In: M.N. Varma and A. Chatterjee (eds): Computational Approaches in Molecular Biology: Monte Carlo Methods. New York: Plenum Press, (1994).
7. R.S. Caswell, Radiat. Res. 27: 92 (1982).
8. M. Zaider, J.F. Dicello, and J.J. Coyne, Nucl. Instr. Meth. B40/41: 1261-1265 (1989).
9. M. Zaider and G.N. Minerbo, Phys. Med. Biol. 33: 1273-1284 (1988).

This research was supported in part by the U.S. Department of Energy under Contract DE-AC02-76CH00016.

Fig.1 Solid lines: $F(t,D)$ as a function of time at the doses indicated in each panel (in cGy) for 1.5 MeV neutrons. Circles: fraction of animals with malignancies in each time interval ($\Delta t=50$ days).

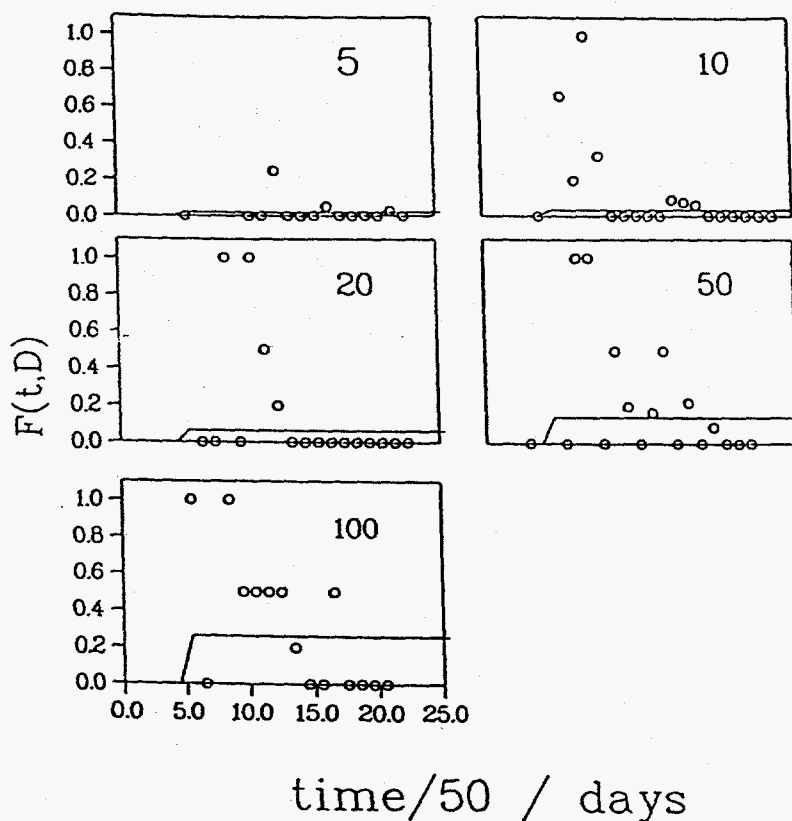


Fig.2 $h(z)$ (solid) and $q(z)$ (dashed) for the induction of myeloid leukemia in mice.

