Multifactorial Analysis of Human Blood Cell Responses to Clinical Total Body Irradiation[1]

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INTRODUCTION

Each source of information which has contributed to our knowledge of human responses to total body irradiation has characteristic advantages and disadvantages. For example, the people exposed to atomic bomb radiations in Hiroshima and Nagasaki were random samples from a presumably normal population, but estimation of the precise radiation dose that each individual received is difficult, and the confounding effects of blast and heat have made it nearly impossible to obtain an accurate dose-response relationship (1). For the analysis of data from patients given therapeutic exposures, the situation is exactly the reverse: dosimetry and clinical follow-up have been extensive, but the patients constitute a nonrandom sample whose usefulness in making extrapolations to the population at large may be seriously questioned. If precise response patterns can be determined for a variety of disease states, it may be possible eventually to combine these estimates with our knowledge of the disease processes and thereby to arrive at a rational prediction of the average radiation response of normal individuals.

Toward this end, a variety of investigators have attempted to describe the average radiation response of the patient given total body therapeutic exposures (2, 3), but none has been able to estimate the radiation response within acceptable confidence limits. This has resulted largely from the fact that therapeutic exposures are often complex combinations of total exposure, number of fractions, and time between fractions, and very few individual patients have received exactly the same combination. The individuality of clinical records prevents the construction of discrete "treatment groups" for dose-response analysis, so pooling procedures are required, such as separating patients who received their total exposure in less than 8 days from those who were exposed over longer periods (2). While this type of treatment may be adequate for gross responses, it has proved to be totally unsuitable for analysis of human blood cell responses.

Standard techniques are available (4), however, which allow the simultaneous study of the effects of total exposure, independent of the time factor, and the effects of time, independent of the total exposure factor. These multiple regression analyses have been applied successfully to the study of the effects of exposure, number of fractions, and time on such quantal responses as tumor control (5) and skin injury (6). The present report demonstrates the potential of these methods for the analysis of human blood cell responses and provides preliminary estimates of the effects of total amount of exposure and time of protraction in determining the minimum white blood cell (WBC) concentration observed after exposure of patients from four disease groups.

MATERIALS AND METHODS

More than 2700 clinical records of patients who had received single or fractionated total body exposures for a variety of diseases were collected from more than 30 participating hospitals (2). Deletion of records that contained inadequate exposure or response information reduced this number to approximately 1000. Additional requirements were imposed on the records for the purposes of the present analysis: only those records which were for the first treatment a patient received were included, since we have preliminary indications that the responses to second and later exposures differ slightly from the responses to first exposures; records for patients who received total exposures of less than 50 R were deleted due to the

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questionable nature of the responses observed; records from those patients in whom the minimum concentration could not be determined with certainty were omitted [in order to be considered a true minimum, the concentration must persist for a reasonable period of time or be followed by an elevated concentration other than the occasionally observed abortive rise (7)]; and disease categories in which there were fewer than ten records were omitted. These qualifications removed all but 518 records, which were distributed among four disease categories: chronic myelogenous leukemia or CML (131 records); chronic lymphatic leukemia or CLL (200 records); lymphosarcoma or LSAR (66 records); and diseases which have no direct effects on the blood-forming tissues or NORMAL (121 patients). The NORMAL group is normal only in a relative sense and includes patients with disseminated solid tumors, as well as patients in the late stages of nonmalignant diseases of the bones, joints, and genitourinary system.

Data were stored and analyzed on a simple time-sharing computer system (Call-A-Computer, Raleigh, North Carolina), which proved entirely adequate for the requirements of this study.

RESULTS

Table I summarizes the number of patients in each disease category who were given single or multiple exposures. We were unable to obtain any data on CLL patients who had received single exposures in excess of 100 R, so a meaningful analysis of their single-exposure response curve could not be conducted.

Table I

Disease category	Single exposures	Multiple exposures
Chronic myelogenous leukemia (CML)	15	116
Chronic lymphatic leukemia (CLL)	—	200
Lymphosarcoma (LSAR)	16	50
NORMAL[a]	92	29

Numbers of patients in each of the four disease categories studied who received single and multiple total body exposures.
[a]Patients with diseases that have no direct effects on blood-forming tissues.

Table II summarizes the exposure and response data for patients from the three disease categories in which a single-exposure analysis could be performed. The mean total exposure varies among the three diseases, reflecting the differences in accepted treatment levels for each of the diseases.

Table II

	NORMAL[a]	CML	LSAR
No. of patients	92	15	16
Mean total exposure	195 R	117 R	108 R
Mean WBC at nadir	21.6%	27.7%	39.9%
Predicted tolerated exposure	19 R	18 R	34 R
Slope (WBC/E)	$-1.04 \pm .16$[b]	$-0.99 \pm .19$[b]	$-1.12 \pm .65$
Correlation coefficient	0.572[c]	0.823[d]	0.419

Exposure and response data for patients from three disease categories who were given single therapeutic exposures.
[a]Patients without diseases which have direct effects on their blood-forming tissues.
[b]$P < 0.001$.
[c]$P < 0.0005$.
[d]$P < 0.005$.

The data for each disease were fit to a variety of equations, with the most satisfactory being a simple power function,

$$\% \text{ WBC} = k\,[100]\,[E]^{\alpha}$$

where % WBC is the WBC count at the nadir as a percentage of the preirradiation levels, k is a constant, E is the midline air exposure in R, and α is the slope of % WBC on E.

Individual slopes were tested for significance by use of t-tests, and the overall correlation coefficient by use of F-ratios (4). The slopes and correlation coefficients are highly significant for the NORMAL and CML groups (Table II), but not for the LSAR group. In each case, however, the slope does not differ significantly from -1.0, indicating that with response measured as the nadir concentration of white blood cells there is no demonstrable difference in radiosensitivity among these three groups, once the tolerated exposure has been exceeded. The predicted tolerated exposure is given by

$$\text{Predicted tolerated exposure} = \text{EXP}\left(\frac{\log k - \log 100}{\alpha}\right).$$

Figure 1 gives the plot of % WBC concentration at the nadir as a function of radiation exposure for the three disease categories. The displacement of the LSAR group to a higher exposure level is not statistically significant and requires further study.

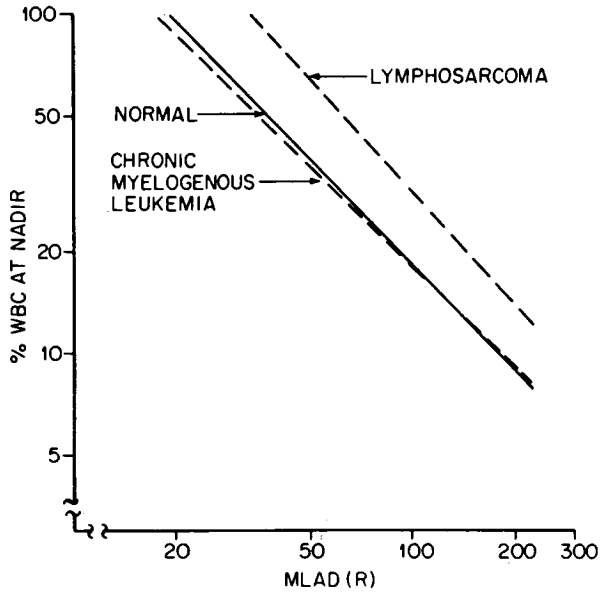

Figure 1. Percent white blood cell concentration at the nadir as a function of radiation exposure for patients with chronic myelogenous leukemia (CML), lymphosarcoma (LSAR), or without any disease which has direct effects on the blood-forming tissues (NORMAL).

For the analyses of multiple exposures we define the time of protraction as the number of days over which the exposure is given. For example, a patient who received one fraction on each of two consecutive days would have a protraction time of two days. Table III summarizes the exposure and response data for patients from the four disease categories who received multiple exposures. Mean total exposures are logically greater, since the exposures were protracted over times of 27 to 36 days on the average. As was the case with the single-exposure data, the most adequate fit proved to be a power function:

$$\% \text{ WBC} = k\,[100]\,[E]^{\alpha}\,[T]^{\beta},$$

where T is the time of protraction in days and ß is the slope of % WBC at a given E on T. The slope of % WBC on exposure does not differ among the NORMAL, CML, and LSAR groups in this multiple-exposure analysis, and it is essentially equal to -1.0, as was observed in the single-exposure groups (Table II). Theoretically, the identity of slopes in the two sets of data is expected, since by our definition the protraction time in the single-exposure studies is one day, and one raised to any power equals one. In other words, the single-exposure data should fit the multiple-exposure equation with T set equal to one. This indicates, therefore, that there are no qualitative differences between the two sets of data (single versus multiple exposure).

Table III

	NORMAL	CML	LSAR	CLL
No. of patients	29	116	50	200
Mean total exposure (E)	233 R	152 R	217 R	116 R
Mean duration of exposure (T)	27.9 days	28.9 days	32.1 days	36.9 days
Mean WBC at nadir	55.2 %	44.4 %	43.8 %	52.9 %
Predicted tolerated exposure	16 R	7 R	25 R	11 R
Slope (WBC/exposure)	$-1.07 \pm .39^{b}$	$-0.82 \pm .12^{d}$	$-1.04 \pm .22^{d}$	$-0.75 \pm .08^{d}$
Slope (WBC/time)	$0.63 \pm .24^{c}$	$0.39 \pm .10^{d}$	$0.23 \pm .18$	$0.22 \pm .06^{d}$
Multiple correlation coefficient	0.535^{c}	0.569^{e}	0.567^{f}	0.583^{e}

Exposure and response data for multiple exposures in four patient samples.
[a]Patients without diseases which have direct effects on their blood-forming tissues.
[b]$P < 0.025$. [c]$P < 0.01$. [d]$P < 0.001$. [e]$P < 0.0001$. [f]$P < 0.0005$.

The CLL group, on the other hand, demonstrates a response on exposure slope which is significantly less than -1.0, but which is not significantly different from the slopes observed for the other diseases. We are unable, therefore, to demonstrate any difference among the disease categories studied in the slope of response on exposure.

The slope of WBC concentration on time at a given exposure presents the most interesting of the results obtained from this analysis. At a given exposure the % WBC at the nadir increases as the 0.63 power of the number of days separating the first and last fractions. Figure 2 illustrates this effect for exposures of 60, 100, and 200 R given over periods of 2 to 32 days. In the CML group, the slope of WBC on time, or more loosely the recovery constant, is smaller but not significantly below that of the NORMAL group. The recovery factor for the two diseases which affect lymphatic tissues, LSAR and CLL, are each approximately one-third of that observed in the NORMAL group ($P < 0.5$ and $P < 0.05$, respectively). Figure 3 illustrates this variation in the time factor for the four groups given 100 R in 2 to 32 days.

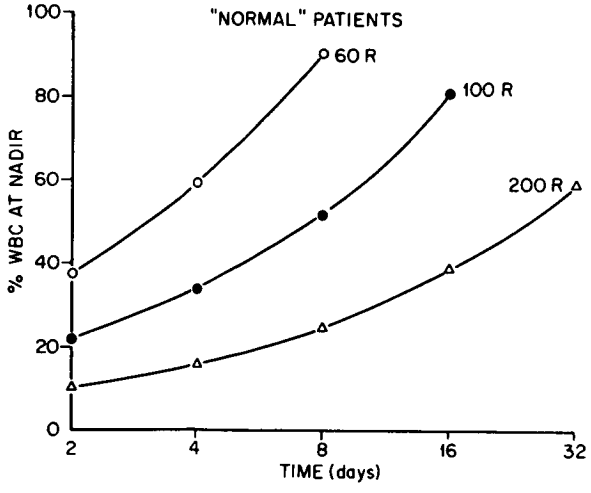

Figure 2. Percent white blood cell concentration at the nadir as a function of radiation exposures of 60, 100, or 200 R given in 2 through 32 days (NORMAL patients).

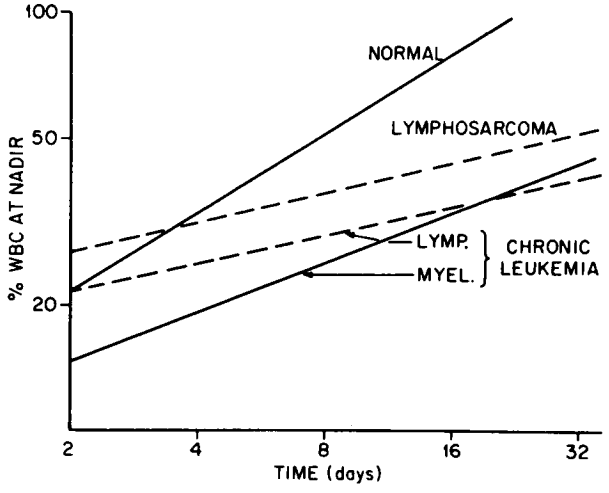

Figure 3. Percent white blood cell concentration at the nadir as a function of the time over which a 100 R exposure is protracted for patients from the four disease categories.

DISCUSSION

It is quite clear from the foregoing that multiple regression analyses can extract important information from complex exposure-versus-response data. It should also be pointed out exactly what this type of analysis cannot do. The data on which these analyses are based cover an exposure range of 50 to 1000 R given over 1 to nearly 100 days. Since we are dealing at present with dividing cell populations which are subject to a variety of dose- and time-dependent compensatory mechanisms, it is clear that any inferences regarding the effects of other exposure patterns must be confined to the range of exposures and times from which the equations have been derived. The analyses do not provide a means of estimating average responses to exposures less than 50 R accumulated in times in excess of 100 days.

In the present report we have considered only two variables: total exposure and time. The number of fractions in which the total exposure was delivered was deleted for two reasons: it would require more space than is available to us to discuss this factor adequately, and the number of fractions and time of protraction are closely correlated. Even with this simple two-factor analysis we have uncovered certain characteristics of the radiation response which obviously merit further study. Two observations, in particular, should be pointed out.

First, there is very little variation among the disease states in regard to the sensitivity to exposure level (cf. Tables II and III). This might appear to contradict the well-established radiosensitivity of the mature lymphocyte (8), but it should be remembered

that response in the present study does not refer to the rate at which the white blood cells disappear from the circulation. Response is measured as the lowest concentration following exposure, independent of the amount of time required to reach this nadir. The radiosensitivity of the progenitor compartments is more important in the determination of the nadir concentration than is the radiosensitivity of the mature element, and our preliminary data are compatible with a conclusion of equal radiosensitivity in the progenitor compartment of the four disease categories.

The fact that the sparing factor associated with protraction of the exposure in time varies as a function of the disease state is quite clear, at least for comparing diseases that affect the lymphatic tissues with those that do not. This corresponds to theoretical expectations (9) as well as to experimental data from lower animals (10) regarding the effects of exposure protraction on lymphatic versus nonlymphatic blood-forming tissues. We will continue to analyze this time factor in the hope of determining what, if any, correlations exist between human and lower animal responses to similar exposure regimens.

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