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Radiosensitivity and Recovery Potential of Human Blood-Forming Tissues:Comparison of Malignant and Nonmalignant States^{1,2}

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ABSTRACT — We studied the peripheral white blood cell response in patients exposed to total-body radiation therapy for one of four diseases: chronic myelogenous leukemia, chronic lymphatic leukemia, lymphosarcoma, and diseases which have no direct effects on the blood-forming tissues. By using the white blood cell count at its nadir as a function of both exposure and protraction time it was determined that no significant differences exist among the four disease states in terms of the radiosensitivity of those tissues which give rise to the peripheral white blood cells. In contrast, the recovery potential of the patients with lymphatic neoplasms was threefold lower than that of the patients with a disease not directly affecting the blood-forming tissues. These data support, therefore, the proposal that fractionation of the total exposure can preferentially allow recovery of normal tissues, at least in the limited sense studied.

INDEX TERMS: Blood Cells • Radiation • Recovery • Fractionation • Man

The largest single doses of ionizing radiation that can be tolerated by a patient's normal tissues are often too small to control effectively the malignancy for which radiation therapy was prescribed. A variety of methods have been proposed to circumvent this problem, including the use of either fractionated or chronic exposures. The rationale for using long-term small exposures is that, under appropriate conditions, it should be possible to obtain greater recovery in normal than in malignant tissues and thereby shift the net injury balance in these two tissues in favor of effective therapy. The critical assumption involved in this rationale is that normal tissues will recover more rapidly than malignant ones. As part of a continuing study of the response of humans to total-body irradiation (1), we report here our analyses of the radiosensitivity and recovery potential of the blood-forming tissues of patients who possessed one of three malignant neoplasms or had a disease that did not directly affect the blood-forming tissues.

MATERIALS AND METHODS

From the clinical records of more than 2700 patients who had received either single or fractionated total-body exposures of x- or gamma-rays (1), we selected 518 of the records by the following criteria: that they include accurate dosimetric information and extensive clinical follow-up; that they concern patients being treated for one of four selected categories of disease; and that they be from patients receiving their first radiotherapeutic treatment or treatments to a total, in either case, of no less than 50 R.

The endpoint measured was the minimum concentration of white blood cells following exposure. In order to be considered a true minimum the concentration must have persisted for a reasonable period of time or have been followed by an elevated concentration other than the occasionally observed abortive rise (2).

The 518 clinical records were distributed among four disease categories: chronic myelogenous leukemia (CML) — 131 records, chronic lymphatic leukemia (CLL) — 200 records, lymphosarcoma (LSAR) — 66 records, and diseases which have no direct effects on the blood-forming tissues (NORMAL) — 121 records. 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.

RESULTS

Single-Exposure Cases: 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 summarizes the exposure and response data for patients from the other three categories. The data for each disease were fit with a variety of equations, with the most satisfactory being a simple power function of the form:

$$\% \text{ WBC} = k(100) (E)^{\alpha}$$

where % WBC is the white blood cell count at its lowest point, expressed as a percent of preirradiation values; k is a constant; E is the midline air exposure in R; and α is the slope of % WBC on E.

(T-I)

The slopes and correlation coefficients are highly significant for the NORMAL and CML groups (TABLE I), but not for the LSAR group, presumably due to the limited exposure range covered by our data. In each case, however, the slope does not differ significantly from -1.0, indicating that, with response measured as the lowest concentration of white blood cells, there is no demonstrable difference in radiosensitivity among these three groups once the tolerated exposure has been exceeded. Figure 1 gives the plot of percent of WBC concentration at the nadir as a function of radiation exposure for the three disease categories. Our data on the displacement of the LSAR group or its greater predicted tolerated exposure is not statistically significant so far and therefore requires further study.

(F-1)

Fractionated-Exposure Cases: For the analyses of patients who had received fractionated exposures it was necessary to use multiple regression techniques (3) so that both exposure and time could be simultaneously considered. We define the time of protraction, T , as the number of days over which the exposure, E , was given. For example, a patient who received one fraction on each of two consecutive days would have a protraction time of two days.

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 % WBC, k , E , and α are as above; T is the time of protraction; and β is the slope of % WBC survival on T , or more loosely, the recovery constant. The slope of percent WBC on exposure (α) does not differ among the NORMAL, CML, and LSAR groups, and is essentially equal to -1.0 (TABLE II), as was observed in the

(T-II)

single-exposure groups (TABLE I). Theoretically, the identity of the slopes in the two sets of data is expected since, by our definition, the protraction time in the single exposure group 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.

The CLL group, on the other hand, demonstrates a response on exposure slope (α) 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 groups in terms of radiosensitivity.

The slope of WBC concentration on time (β) at a given exposure provides the most interesting of the results obtained in this analysis. At a given exposure, the percent WBC at the nadir increases as the 0.63 power of the protraction time for the NORMAL group. Figure 2 illustrates this effect for exposures of 60, 100, and 200 R.

(F-2)

In the CML group, this recovery constant (β) is smaller but not significantly below that of the NORMAL group. The recovery factors for the two diseases which affect the lymphatic tissues, LSAR and CLL, are each approximately one-third of that observed in the NORMAL group ($P < .5$ and $P < .05$, respectively). Figure 3 illustrates this variation in the recovery constant among the four groups at an exposure level of 100 R.

(F-3)

DISCUSSION

In this report we have considered only two variables: exposure and time. Even with this simple analysis we have uncovered certain characteristics of the radiation

response which obviously merit further investigation. Two observations in particular should be noted. First, there is little variation among the disease states in terms of the radiosensitivity of those tissues which give rise to the white blood cells (TABLES I and II). This might appear to contradict the well-established radiosensitivity of the mature lymphocyte (4), but it should be remembered that "response" in the present study does not refer to the rate at which the WBC disappear from the circulation, but rather to the lowest concentration following exposure. The radiosensitivity of the progenitor compartments is more important to this endpoint than is the radiosensitivity of the mature element, and our preliminary data are compatible with a conclusion of equal radiosensitivity in the progenitor compartments of the four diseases studied.

The fact that the reduced effectiveness of radiation associated with protraction of the exposure in time varies as a function of the disease state is quite clear, at least for comparison of those diseases which affect the lymphatic tissues with those that do not. These data support the proposal that radiotherapy of malignant neoplasms of lymphatic tissues may best be accomplished through the use of protracted exposures (5).

Clearly, additional variables must be included before a quantitative interpretation can be made of these data. We are currently expanding our studies to include additional disease states, as well as further exposure variables such as number of fractions and fraction size.

Even at this preliminary stage, however, it is evident that protraction of the exposure in time may be a most efficient means of treating these refractory neoplasms of the lymphatic tissues.

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TABLE I. EXPOSURE AND RESPONSE DATA FOR PATIENTS FROM THREE DISEASE CATEGORIES WHO WERE GIVEN SINGLE EXPOSURES IN EXCESS OF 50 R

	NORMAL*	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 of WBC on E (α)	$-1.04 \pm .16^\dagger$	$-0.99 \pm .19^\dagger$	$-1.12 \pm .65$
Correlation coefficient	0.572 [‡]	0.823 [§]	0.419

* Patients with diseases which do not have direct effects on the blood-forming tissues.

[†] $p < .001$

[‡] $p < .0005$

[§] $p < .005$

TABLE II. EXPOSURE AND RESPONSE DATA FOR PATIENTS FROM FOUR DISEASE CATEGORIES WHO RECEIVED MULTIPLE EXPOSURES

	NORMAL*	CML	LSAR	CLL
No. of patients	29	116	50	200
Mean total exposure (E)	233 R	152 R	217 R	116 R
Mean protraction time (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%
Slope (WBC/E) or α	$-1.07 \pm .39^{\dagger}$	$-0.82 \pm .12^{\delta}$	$-1.04 \pm .22^{\delta}$	$-0.75 \pm .08^{\delta}$
Slope (WBC/T) or β	$0.63 \pm .24^{\ddagger}$	$0.39 \pm .10^{\delta}$	$0.23 \pm .18$	$0.22 \pm .06^{\delta}$
Multiple correlation coefficient	0.535 [‡]	0.569 [¶]	0.567	0.583 [¶]

* Patients with diseases which do not directly affect the blood forming tissues.

[†] $P < .025$

[‡] $P < .01$

[§] $P < .001$

[¶] $P < .0001$

^{||} $P < .0005$

FIGURE LEGENDS

Fig. 1. Percent concentration of white blood cells at their nadir as a function of single exposure level in patients from three of four disease categories studied.

No records were available for chronic lymphatic leukemia.

Fig. 2. Percent concentration of white blood cells at their nadir in NORMAL patients following 60, 100, or 200 R as a function of the time over which the exposures were given.

Fig. 3. Percent concentration of white blood cells at their nadir as a function of time over which a 100-R exposure was given in patients from the four disease categories studied.

24764

Fig. 1

24762

Fig. 2

24763

Fig. 3