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COMMENTARY

The Risk of Chronic Myeloid Leukemia: Can the Dose–Response Curve be U-Shaped?

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Chronic myeloid leukemia (CML) is caused by a *BCR-ABL* chromosome translocation in a primitive hematopoietic stem cell. The number of hematopoietic stem cells in the body is thus a major factor in CML risk. Evidence suggests that the number of hematopoietic stem cells in the body is only loosely regulated, having a broad "dead-band" of physiologically acceptable values. The existence of a dead-band is important, because it would imply that low levels of hematopoietic stem cell killing can be permanent; i.e., it would imply that low doses of ionizing radiation can cause permanent reductions in the total number of CML target cells and thus permanent reductions in the subsequent risk of spontaneous CML. Such reductions in risk could be substantial if hematopoietic stem cells are also hypersensitive to radiation killing at low dose. Our calculations indicate that, due to dead-band hematopoietic stem cell control, if hematopoietic stem cells are as hypersensitive to killing at low doses as epithelial cells, reductions in the *spontaneous* CML risk could exceed the low-dose risks of *induced* CML; i.e., the net lifetime CML risk could have a U-shaped dose–response curve.

INTRODUCTION

Chronic myeloid leukemia (CML) is ideal for biologically based modeling of low-dose radiation cancer risk because it is molecularly defined, unequivocally radiogenic, and well understood (*1, 2*). Giving a detailed, mechanistic explanation of this unique cancer seems possible, would be important for its own sake, and could perhaps cast light on radiation carcinogenesis in general.

It is now well accepted that CML is caused by a *BCR-ABL* chromosome translocation in a primitive hematopoietic stem cell (*3*). The number of hematopoietic stem cells in the body is consequently a major factor in CML risk. There are at least four papers suggesting that hematopoietic stem cell numbers are only loosely regulated. In the first paper (*4*), bone marrow transplant doses of 10, 100 and 1000 long-term competitive repopulating units (CRU) injected into congenic irradiated recipient mice yielded a functional hematopoietic system at each dose. The reconstituted CRU levels lay anywhere from 1–20% normal, or 15–60% normal, depending on the dose and origin (bone marrow or fetal liver, respectively) of the injected CRU. These results suggest that CRU expand more at low doses than at high doses, and that high doses overshoot the requisite hematopoietic stem cell number, leaving the final hematopoietic stem cell level anywhere within a ''dead-band'' of physiologically acceptable values; here ''dead'' refers to the alleged nonresponsive character of the hematopoietic stem cell control system. In the second paper, broad interindividual variation in hematopoietic stem cell levels was observed (*5*), as would be expected if hematopoietic stem cells were only loosely regulated. Finally, consistent with hematopoietic stem cells repopulating only up to the bottom of a putative dead-band, bone marrow transplant patients with fully functional hematopoietic systems have permanently reduced hematopoietic stem cell levels (*6, 7*). Intuitively, if only a fraction of the hematopoietic stem cells are needed to sustain a fully functional hematopoietic system, the rest being a reserve, it seems plausible that a small hematopoietic stem cell loss would not be recovered, since there would be no loss-of-function feedback signal to drive the hematopoietic stem cell level back to its original value.

This commentary discusses the implications of dead-band hematopoietic stem cell control if hematopoietic stem cells are also hypersensitive at low doses (*8*) to killing by ionizing radiation. We use a previously analyzed model of CML risk (*1*) and a biophysical model of *BCR-ABL* chromosome translocations (*2*).

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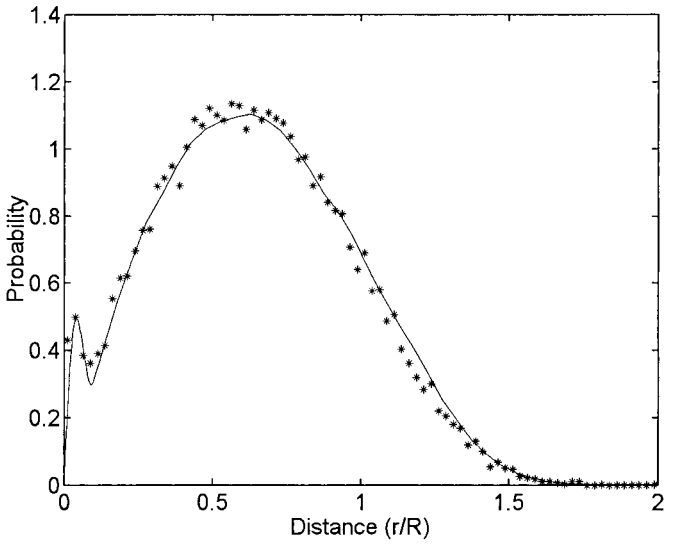

FIG. 1. Lymphocyte 2D *BCR*-to-*ABL* distances relative to *R*, the radius of the nuclei (*15*).

MODELS

The LQE Model

The linear-quadratic-exponential (LQE) dose–response model of CML risk (*1*) is

$$m = \left[e^{c_1+ka} + \left(D_\gamma + \frac{\beta_{ba}}{\alpha_{ba\gamma}} D_\gamma^2 + \frac{\alpha_{ban}}{\alpha_{ba\gamma}} D_n \right) t^2 e^{c_2+k_1 t} \right] \cdot P e^{-(\alpha_{k\gamma} D_\gamma + \beta_k D_\gamma^2 + \alpha_{kn} D_n)}, \quad (1)$$

where *m, a, P, t,* D_γ and D_n denote the expected number of CML cases, the age, the person-years, the number of years since exposure, and the γ-ray and neutron marrow doses, respectively. Here e^{c_1+ka} is the background incidence as a function of age, $\alpha_{ba\gamma} D_\gamma + \beta_{ba} D_\gamma^2 + \alpha_{ban} D_n$ is the probability of formation of the *BCR-ABL* translocation in an irradiated target cell, $e^{-(\alpha_{k\gamma} D_\gamma + \beta_k D_\gamma^2 + \alpha_{kn} D_n)}$ is the probability that the target cell is not killed (consistent with a dead-band, this factor also multiplies the background incidence), and $t^2 e^{c_2 - k_1 t}$ represents the *BCR-ABL*-to-CML waiting-time probability density multiplied by $N\alpha_{ba\gamma}$, where *N* is the number of CML target cells. Using A-bomb exclusive data, estimates can be obtained for each of the nine parameters of the LQE model. These ''prior'' parameter estimates can then be combined with A-bomb survivor data in a Bayesian approach to CML risk estimation (*1*).

Locus-Specific TDRA

The necessary prior estimates of *BCR-ABL* translocation probabilities can be obtained from a locus-specific adaptation (*2*) of the distance formulation of the theory of dual radiation action (TDRA) (*9*). The adaptation is succinctly summarized by

$$P(ba|D) = 2T_{BCR}T_{ABL}Y^2D \int_0^\infty \frac{t_D(r)}{\rho 4\pi r^2} S_{ba}(r) g(r)\, dr = \alpha_{ba} D + \beta_{ba} D^2, \quad (2)$$

where $P(ba|D)$ is the probability of a *BCR-ABL* translocation per G_0/G_1-phase cell given a dose *D*; $t_D(r)dr$ is the expected energy at distance *r* given an ionization event at the origin; $S_{ba}(r)$ is the *BCR*-to-*ABL* distance probability density; $g(r)$ is the probability that two DSBs misrejoin if they are created a distance *r* apart; $Y = 0.0058$ DSBs/Mb Gy^{-1} (*10, 11*); ρ = mass density; $T_{BCR} = 5.8$ kbp (*12*); and $T_{ABL} = 300$ kbp (*12*).

The integral in Eq. (2) can be understood as follows. Pick one of the two *ABL* loci in a G_0/G_1-phase cell and place it at the origin. The probability that there is a DSB in this locus is the target size of *ABL,* T_{ABL}, multiplied by the DSB yield *Y*, multiplied by the dose *D*. Given that *ABL* is at the origin, the probability that *BCR* is a distance *r* away is $S_{ba}(r)dr$. Given that *BCR* is a distance *r* away, the probability that there is a break in *BCR* is the conditional dose at *r,* $t_D(r)/\rho 4\pi r^2$, multiplied by the DSB yield *Y*, multiplied by the *BCR* target size T_{BCR}; here $t_D(r)$ is conditional on there being an ionization event at the origin, and there must have been an ionization event at the origin since there is a DSB at the origin, the one in *ABL.* Finally, given that these two DSBs in *ABL* and *BCR* were produced a distance *r* apart, the probability that they misrejoin is $g(r)$. Integrating these events over all possible initial separations *r*, the result is the probability that *BCR* and *ABL* misrejoin. The factor of 2 in Eq. (2) results because there are two *ABL* loci and two *BCR* loci (factor of 4) and because only about half the misrejoining events are translocations (factor of ½, the other half being dicentrics). The TDRA is useful because if $t_D(r)$ is calculated based on particle track codes (*13*), and if $g(r)$ is estimated based on dicentric yields (*2, 14*), interlocus distance distributions (*15, 16*) [e.g. $S_{ba}(r)$] can then be converted into dose–response predictions for specific translocations (*2*) and inversions (*17*). Using the *BCR*-to-*ABL* distance distribution in Fig. 1 for $S_{ba}(r)$, the TDRA integral above gave prior estimates of $\alpha_{ba\gamma}$ and β_{ba} which, when combined with A-bomb survivor data, gave the LQE posterior parameter estimates (*1, 2*) used below in forming Figs. 2, 3 and 4.

RESULTS

The net lifetime excess absolute risk of CML is the integral over all years postexposure of the excess CML incidence rate, $\mu(a|x,D)$ minus $\mu(a)$, weighted by the conditional probability $S(a|x,D)$ that a person exposed at age *x* is still at risk at age *a* (*18*); i.e.,

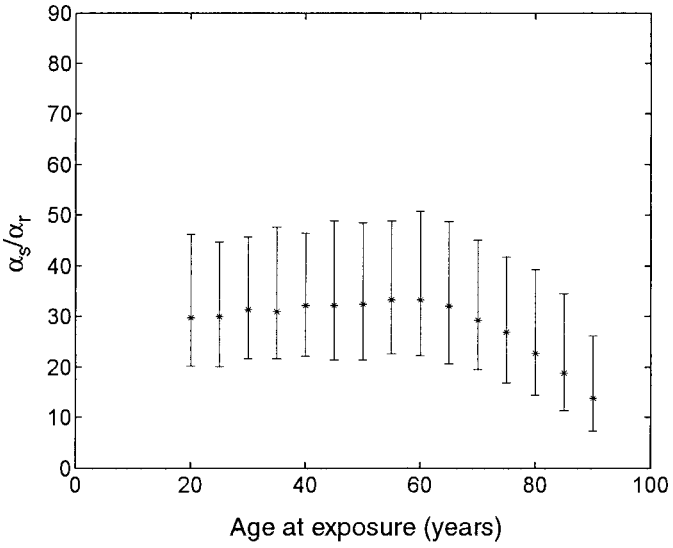

FIG. 2. Hematopoietic stem cell hypersensitivity ratios α_s/α_r needed to produce a zero-slope net lifetime CML risk in the limit of low doses. An LQE posterior estimate of $\alpha_{k\gamma r} = 0.290\ \mathrm{Gy}^{-1}$ (*1*) is assumed.

$$R = \int_x^{y_T} [\mu(a|x, D) - \mu(a)] \cdot S(a|x, D)\, da$$

$$= \int_x^{y_T} \left\{ \left[e^{c_1+ka} + \left(D_\gamma + \frac{\beta_{ba}}{\alpha_{ba\gamma}} D_\gamma^2 + \frac{\alpha_{ban}}{\alpha_{ba\gamma}} D_n \right) \cdot (a - x)^2 e^{c_2 - k_t(a-x)} \right] \cdot e^{-(\alpha_{k\gamma} D_\gamma + \beta_k D_\gamma^2 + \alpha_{kn} D_n)} - e^{c_1+ka} \right\} \cdot S(a|x, D)\, da, \quad (3)$$

where μ is given by the LQE model (Eq. 1). Here we assume the coefficient $\alpha_{k\gamma}$ can change with dose ($\alpha_{k\gamma} = \alpha_{k\gamma s}$ for $D_\gamma < 0.05$ Gy and $\alpha_{k\gamma} = \alpha_{k\gamma r}$ for $D_\gamma > 0.5$ Gy), corresponding to hypersensitivity at low dose for cell killing (*8*); we assume $\alpha_{ba\gamma}$ does not change, because low-dose hypersensitivity has not been observed for translocations. In the equation, D represents the dose pair (D_γ, D_n), but henceforth we consider the case of negligible neutron dose, $D_n = 0$. Then, letting $D_\gamma \to 0$ (i.e. neglecting terms quadratic or higher in D_γ) to get the low-dose risk R_0 gives

$$R \to R_0 = D_\gamma \int_x^{y_T} [(a - x)^2 e^{c_2 - k_t(a-x)} - \alpha_{k\gamma s} e^{c_1+ka}] \cdot S(a|x, 0)\, da. \quad (4)$$

To characterize the amount of low-dose hypersensitivity $\alpha_{k\gamma s}$ needed for a low-dose risk with zero slope, we set R_0 equal to zero and solved for $\alpha_{k\gamma s}$ as a function of exposure age x. We let $y_T = 100$ years, used $S(a|x,0)$ for 1960 U.S. males (*19*), and sampled (c_1, c_2, k, k_t) from its multivariate normal LQE posterior distribution; the posterior used corresponds to row 3 in Table 2 of Radivoyevitch *et al.* (*2*). This was done for exposure ages of 20, 25, . . . 90 years.

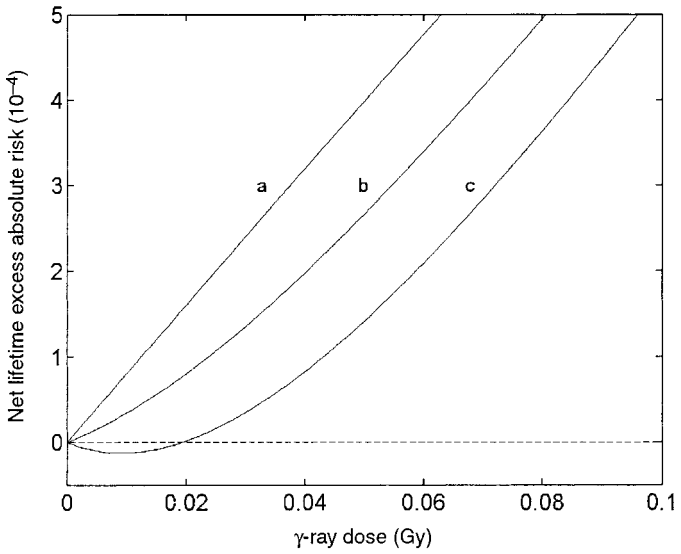

FIG. 3. Net lifetime CML risk for γ rays. Shown are three different types of dose responses: (a) nearly linear ($\alpha_s/\alpha_r = 1$), (b) "hockey-stick" shaped ($\alpha_s/\alpha_r = 20$), and (c) U-shaped ($\alpha_s/\alpha_r = 40$). The different types can give quite different results when extrapolating risk from higher doses to very low doses. Still further types of dose–response curves (e.g. cupped downward) are possible if other effects, not discussed in this Commentary, play an important role at low doses.

The resulting median and 10th and 90th percentiles of $\alpha_{k\gamma s}/\alpha_{k\gamma r}$ are plotted in Fig 2. Since values of $\alpha_{k\gamma s}/\alpha_{k\gamma r}$ as high as 30 are not unreasonable, albeit for epithelial cells (*8*), this plot suggests that a U-shaped dose response (Fig. 3c) is indeed possible for the net lifetime risk of CML. A curve such as that in Fig. 3c, with negative excess risk at low doses, would occur if the target cell hypersensitivity ratios were found to be greater than the values shown in Fig. 2. In generating Fig. 3, we used Eq. (3) with $x = 40$ years, LQE posteriors as in Fig. 2, and $\alpha_{k\gamma} = \alpha_{k\gamma s} e^{-D_\gamma/D_c} + \alpha_{k\gamma r}(1 - e^{-D_\gamma/D_c})$ with $D_c = 0.05$ Gy; although D_c estimates fall

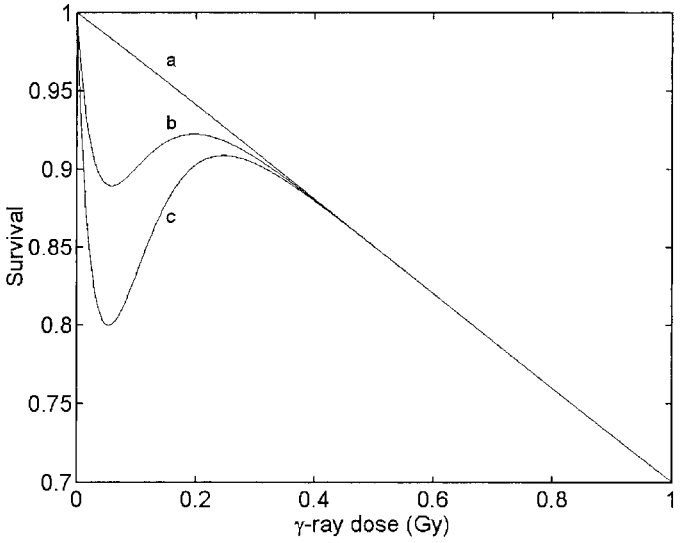

FIG. 4. Surviving fractions (a), (b) and (c) corresponding to Fig. 3.

between 0.1 and 0.3 Gy for 4 different cell lines (*20*), to keep the surviving fraction above 0.8 for doses below 0.5 Gy when $\alpha_{k\gamma s}/\alpha_{k\gamma r} = 40$, we let $D_c = 0.05$ Gy (see Fig. 4).

DISCUSSION

Physiological control of target cells can lie at either one of two extremes. At one extreme, if target cells are functional tissue cells, tight control can be expected since target cell loss would then correspond to tissue function loss. At the other extreme, if target cells are rare stem cells (*21*), loose control might be expected, at least in some cases, since, even though they are rare, stem cells may be abundant relative to the needs of the tissue (see the Introduction). Dead-band control is a conceptual approximation to this latter extreme of loose control.

Our calculations indicate that if hematopoietic stem cells are as hypersensitive to killing by low doses as epithelial cells (*8*), reductions in spontaneous CML risk could partially cancel, completely cancel, or even exceed, the low-dose risks of induced CML. Net lifetime CML risk could thus have a U-shaped dose response (Fig. 3). Dead-band control seems essential to get a significant effect. For tight control instead of dead-band control, reductions in cell numbers due to radiation killing at low doses would be too temporary to reduce spontaneous lifetime risk significantly.

For a U-shaped or ''hockey-stick'' dose response, linear extrapolations from higher doses overestimate low-dose risk (Fig. 3). If many types of cancer have low-dose hypersensitive, dead-band-regulated target cells, the public health implications could be quite significant.

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