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ScienceDirect
Journal of Theoretical Biology 245 (2007) 83–97
Journal of Theoretical Biology
www.elsevier.com/locate/yjtbi

A multi-compartment cell repopulation model allowing for inter-compartmental migration following radiation exposure, applied to leukaemia

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Received 10 April 2006; received in revised form 25 September 2006; accepted 25 September 2006
Available online 1 October 2006

Abstract

There is much uncertainty about cancer risks at the high radiation doses used in radiotherapy (RT). It has generally been assumed that cancer induction decreases rapidly at high doses due to cell killing. However, this is not seen in all RT groups, and a model recently developed by Sachs and Brenner [2005. Solid tumor risks after high doses of ionizing radiation. Proc. Natl Acad. Sci. USA 102, 13040–13045] proposed a mechanism for repopulation of cells after radiation exposure that explained why this might happen, at least for solid tumours. In this paper, this model is generalized to allow for heterogeneity in the dose received, and various alternate patterns of repopulation are also considered. The model is fitted to the Japanese atomic bomb survivor leukaemia incidence data, and data for various therapeutically irradiated groups. Two sets of parameters from these model fits are used to assess the sensitivity of model predictions.

It is shown that in general allowing for heterogeneity in dose distribution and haematopoietic stem cell migration results in lower risks than the same average dose administered uniformly and without such migration, although this does not hold in the limiting case of complete stem cell repopulation between radiation dose fractions. We also investigate the difference made by assuming a compartmental repopulation signal, and a global repopulation signal. In general we show that in the absence of stochastic extinction, compartmental repopulation always predicts a larger number of mutated cells than global repopulation. However, in certain dose regimes stochastic extinction cannot be ignored, and in these cases the numbers of mutated cells predicted with global repopulation can exceed that for compartmental repopulation. In general, mutant cell numbers are highly overdispersed, with variance much greater than the mean.

Keywords: Cancer risk; Radiotherapy; Leukaemia; Stem cells; Repopulation

1. Introduction

The Japanese atomic bomb survivor Life Span Study (LSS) cohort is the principal source of data used to estimate risks of radiation-related cancer (USNAS, 1990, 2006; ICRP, 1991; UNSCEAR, 2000). The A-bomb survivors are unusual among exposed populations in that both sexes and a wide range of ages were exposed, comparable with those of a general population (Preston et al., 2003, 2004). The A-bomb survivors received moderate to low doses of ionizing radiation (average dose ~0.1 sievert). Risks after the much higher radiation dose exposures administered in radiotherapy (RT) are less well understood, although it is clear that in many cohorts risks per unit dose are lower than those in the LSS data (Little et al., 1999; UNSCEAR, 2000; Little, 2001). Nevertheless, in some cohorts cancer risks per unit dose are reasonably similar to those in the LSS cohort (Travis et al., 2003; van Leeuwen et al., 2003; Gilbert et al., 2003), and on the face of it this is puzzling. In RT radiation dose is generally administered in a fractionated protocol, that is to say, one in which the total dose is given in a number of (generally equal) fractions, separated by a few days, to allow time for

Abbreviations: Gy, gray; HSC, haematopoietic stem cell; LSS, Life Span Study; RT, radiotherapy

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doi:10.1016/j.jtbi.2006.09.026

tissue recovery, and thereby to spare normal tissue surrounding the tumour (Thames and Hendry, 1987). Because of this, the total dose in a nearby organ resulting from a fractionated protocol can be quite high, in excess of 20 gray (Gy) (Travis et al., 1997, 2000, 2002, 2003; Little, 2001; van Leeuwen et al., 2003). At doses as high as this, cell killing becomes important (and without fractionation would certainly result in sterilization of the irradiated tissue volume (Thames and Hendry, 1987)), and unless some mechanism compensates for killing one would expect very few live cells in the affected region and correspondingly little second cancer risk.

Sachs and Brenner (2005) proposed a model for cell repopulation after RT that can satisfactorily account for the similarity in solid tumour risks in RT and LSS datasets. Sachs and Brenner (2005) did not model second leukaemia risk. In general the risk of leukaemia per unit dose is much lower in RT cohorts than in the LSS (Little, 2001), implying that repopulation must be less effective for this endpoint, or that there are other mechanisms playing a part. Repopulation of haematopoietic stem cells (HSC) is known to be rapid after RT (Sheridan et al., 1992; Bensinger et al., 1993), and has also been demonstrated in non-human primates after high dose total body irradiation (Farese et al., 2003).

One feature of most RT regimes not taken into account in the model of Sachs and Brenner (2005) is dosimetric heterogeneity. Absorbed doses in different locations in the bone marrow are dramatically different, varying by factors of up to ~1000 from one location to another (Stovall et al., 1989). A complication with leukaemia that does not apply to most solid cancers is that the relevant stem cells are disseminated in bone marrow around the body. It is known experimentally that HSC are recruited to and cleared from the blood, in part a consequence of cytokine exposure (Wright et al., 2001; Abkowitz et al., 2003; Lapidot et al., 2005). In particular, HSC migration is known to take place after RT. The speed with which it does so is uncertain, ranging from minutes or hours (Wright et al., 2001) to days (Abkowitz et al., 2003); this is therefore not necessarily much different from the speed of in situ HSC doubling in bone marrow, which typically takes days to weeks (Möbest et al., 1999; Ashihara et al., 2002; Flores-Guzmán et al., 2002; Farese et al., 2003; Oredipe et al., 2003; Yan et al., 2003; Iwama et al., 2004; Martínez-Jaramillo et al., 2004). Because the migration of HSCs from less-damaged parts of the bone marrow will generally result in fewer mutant cells being produced, the expectation is that such a process would reduce leukaemia risks. Stem cell migration is also not taken into account in the model of Sachs and Brenner (2005).

In this paper, the repopulation model of Sachs and Brenner (2005) is generalized to allow for a number of inter-communicating stem cell (HSC) compartments, which allows for heterogeneity in the dose received. (If dose is administered uniformly there is no need for a multi-compartment model such as this, since all parts of a tissue are damaged equally). We consider various alternate patterns of repopulation and stem cell migration. In particular, we assess the difference made by assuming locally rather than globally controlled repopulation. We also consider the difference made by models that assume HSC migration, whether via the blood or directly, compared with models that do not assume such migration. The reason for exploring such a variety of models is to assess the effect these have on the predicted risks; in some cases there is little or no evidence to favour one model over another model, but for this reason, it is essential to determine the difference made for predictions. Most of the models developed are general in form, and a lot of the development would be relevant to any tissue. However, the development is largely motivated by leukaemia, and parameters used in simulations are obtained via fits to the LSS and other (RT) leukaemia data.

2. Model assuming compartmental repopulation process, without stem cell migration

We first consider a simple model, a straightforward generalization of the model of Sachs and Brenner (2005), which assumes that there are L tissue compartments in the organ being irradiated, and with no communication between compartments. This model is probably of most application to solid cancers; for leukaemia, where HSC migration is known to take place, it is arguably less realistic. Nevertheless, it is worthwhile to consider it (and a closely related model with a global rather than compartmental repopulation signal) in order to demonstrate the role played by HSC migration. Let $n_i(t,(d_{ij}))$ be the number of cells in compartment i that are normal, and $m_i(t,(d_{ij}))$ be the number of cells in compartment i that are mutated at time t; we shall often abbreviate these for simplicity as $n_i(t)$ and $m_i(t)$, respectively. Assume that the radiation dose for compartment i is given in k fractions, with dose d_{ij} being given at time t_{ij} (jth fraction), $1 \leqslant j \leqslant k$. We assume that between radiation doses:

$$\frac{\mathrm{d}n_i}{\mathrm{d}t} = \lambda n_i\left[1-\frac{n_i}{N_i}\right],$$
$$\frac{\mathrm{d}m_i}{\mathrm{d}t} = \lambda r m_i\left[1-\frac{n_i}{N_i}\right] \quad (1)$$

in other words, that repopulation in each compartment proceeds independently of each other compartment, at a rate equal to λ per cell per unit time, multiplied by $1-(n_i/N_i)$. This last factor serves to limit cell repopulation in the normal cell compartment, so that $\lim_{t\to\infty} n_i(t) = N_i$. N_i is the (asymptotic limiting) number of cells in compartment i, and r is the per-cell repopulation rate for mutated cells relative to normal cells. Writing $n_i(t_{ij}-) = \lim_{t\uparrow t_{ij}} n_i(t)$, and $n_i(t_{ij}+) = \lim_{t\downarrow t_{ij}} n_i(t)$, in other words the limits of $n_i(t)$ from below and above t_{ij}, respectively, and likewise for $m_i(t_{ij}-)$