Non-Targeted Effects and the Dose Response for Heavy Ion Tumorigenesis

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Abstract

BACKGROUND

There is no human epidemiology data available to estimate the heavy ion cancer risks experienced by astronauts in space. Studies of tumor induction in mice are a necessary step to estimate risks to astronauts. Previous experimental data can be better utilized to model dose response for heavy ion tumorigenesis and plan future low dose studies.

DOSE RESPONSE MODELS

The Harderian Gland data of Alpen et al. [1-3] was reanalyzed [4] using non-linear least square regression. The data set measured the induction of Harderian gland tumors in mice by high-energy protons, helium, neon, iron, niobium and lanthanum with LET ranging from 0.4 to 950 keV/micron. We were able to strengthen the individual ion models by combining data for all ions in a model that relates both radiation dose and LET for the ion to tumor prevalence. Compared models based on Targeted Effects (TE) to one motivated by Non-targeted Effects (NTE) that included a bystander term that increased tumor induction at low doses. When comparing models to the experimental data, we adjusted the $R^2$, the Akaike Information Criteria (AIC), and the Bayesian Information Criteria (BIC) to test for Goodness of fit. In the adjusted $R^2$ test, the model with the highest $R^2$ values provides a better fit to the available data. In the AIC and BIC tests, the model with the smaller values of the summary value provides the better fit. The non-linear NTE fits the combined data better than the TE models that are linear at low doses.

We evaluated the differences in the relative biological effectiveness (RBE) and found the NTE model provides a higher RBE at low dose compared to the TE model.

Power Analysis

The final NTE model estimates were used to simulate example data to consider the design of new experiments to detect NTE at low dose for validation. Power analysis and sample sizes were calculated for a variety of radiation qualities including some not considered in the Harderian Gland data set and with different background tumor incidences. We considered different experimental designs with varying number of doses and varying low dose dependent on the LET of the radiation. The optimal design to detect an NTE for an individual ion had 4 doses equally spaced below a maximal dose where “bending” due to cell sterilization was <2%. For example at 100 keV/micron we would irradiate at 0.03 Gy, 0.065 Gy, 0.13 Gy, and 0.26 Gy and require 550 mice including a control group to detect differences with 80% power. Sample sizes could be improved by combining ions similar to the methods used with the Harderian Gland data.

Color Categories

Uncertainty Reduction/Risk Mitigation Category Color = Green
Mechanistic/Descriptive Category Color = Light Yellow

Heavy Ions TE model relating dose and LET to tumor prevalence

$P_{TE} = P_0 + (aD + bD^2)e^{cLD}$

<table>
<thead>
<tr>
<th>Dose induction term</th>
<th>Cell sterilization term</th>
<th>TE estimate</th>
<th>Standard Error</th>
<th>$\alpha$</th>
<th>$\beta$</th>
<th>$\lambda$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_0 = 2.64$</td>
<td>$a = 0.47$</td>
<td>$b = 0.07$</td>
<td>$\lambda = 0.24$</td>
<td>0.056</td>
<td>0.056</td>
<td>0.056</td>
</tr>
</tbody>
</table>

Heavy Ions NTE model relating dose and LET to tumor prevalence

$P_{NTE} = P_0 + \alpha(D)e^{\lambda(D)}$ + $\kappa(\lambda_0 + \lambda_0 e^{\lambda_0 D})$

<table>
<thead>
<tr>
<th>LET</th>
<th>$P_{NTE}$</th>
<th>$P_{TE}$</th>
<th>$P_0$</th>
<th>$\alpha$</th>
<th>$\lambda$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.03 Gy</td>
<td>0.065 Gy</td>
<td>0.13 Gy</td>
<td>0.26 Gy</td>
<td>0.03 Gy</td>
<td>0.065 Gy</td>
</tr>
</tbody>
</table>

Power Analysis Specifications

- The study focuses on low doses where the cell sterilization term can be ignored.
- Power analysis and sample sizes were calculated for a variety of radiation qualities including some not considered in the Harderian Gland data set and with different background tumor incidences. We considered different experimental designs with varying number of doses and varying low dose dependent on the LET of the radiation. The optimal design to detect an NTE for an individual ion had 4 doses equally spaced below a maximal dose where “bending” due to cell sterilization was <2%.
- Simulations were analyzed using generalized linear models with binomial errors following the low dose model.

Table: Sensitivity of sample size to detect NTE with 80% power to the scheme choice and background in Prevalence ($P_0$).

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Fe, LET = 70</th>
<th>Fe, LET = 100</th>
<th>Fe, LET = 193</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose A1</td>
<td>900 Gy</td>
<td>1010 Gy</td>
<td>690 Gy</td>
</tr>
<tr>
<td>Dose A2</td>
<td>810 Gy</td>
<td>1061 Gy</td>
<td>1810 Gy</td>
</tr>
<tr>
<td>Dose A3</td>
<td>1101 Gy</td>
<td>1810 Gy</td>
<td>&gt;4379 Gy</td>
</tr>
</tbody>
</table>

Power Analysis Conclusions

- Dosing Scheme 3 was optimal.
- More mice are needed as the value of $P_0$ increases.

Cross-over dose is defined as the dose where TE = NTE

Equation: The individual NTE Model

$P_{NTE} = P_0 + \alpha(D) + \kappa(D)$

Equation: The linear low dose model

$P_{TE} = P_0 + aD + bD^2$