Reviewer's report

Title: Cell Killing and Resistance in Pre-Operative Breast Cancer Chemotherapy

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Reviewer: Alberto Gandolfi

Reviewer's report:

General

The paper presents an analysis of the effect of a pre-operative breast cancer treatment on a set of thirty-five patients. By means of a mathematical model of the tumour response, from measurements of tumour volume at different times and of the growth fraction (GF) at the start of treatment, the authors were able to estimate the surviving fractions of proliferating and quiescent cells after the single dose. A parameter related to the presence of drug resistance was also estimated in a subset of patients. A finite number of different cell kinetics scenarios compatible with the measured GF were hypothesized, and the final estimate of cell killing was assessed through the use of the likelihood ratio test and of the parsimony principle. The work is original and valuable, showing how a careful use of mathematical modelling can extract from data information not otherwise available. The paper is clearly written, and is acceptable after the few revisions listed.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. p. 5, last line. The parameter \( \mu \) is the rate constant of death, not the "probability of death". More precisely, \( \mu \times dt \) is the probability to die in the time interval \( dt \). The same can be said for the parameter \( \gamma \).

2. p. 15. In the equation for \( N_p(t) \), it seems to me that \( N_q(t-\Delta) \) should be multiplied by \( \gamma \times \Delta \) (and not by \( \gamma \times z \)). Similarly, in the equation for \( N_q(t) \), \( N_q(t-\Delta) \) should be multiplied by \( (1-\Delta \times (\gamma+\mu)) \). The original equation for \( N_q \) is an ordinary differential equation indeed.

4. Table 1. In the Level III row (and in the legend), the parameters are indicated as Sp, Sq, Sp1, Sq1, whereas at pp. 7 and 16 they are Sp, Sq, Sp2, Sq2.

Discretionary Revisions (which the author can choose to ignore)

5. The mean and the standard deviation of the measured GF value might be reported (in the "Patients and histology" section).

6. The estimated value of k (the parameter related to the delay in the loss of dead cells) is of interest and might be reported.

7. For the nine patients in which the sensitivity switch was detected, it would be interesting to provide some information on the time when this switch occurred.

8. Appendix 1. The equations for Np and Nq appear to be derived by assuming an exponential age distribution for the proliferating cells. During the treatment, if $\gamma>0$, this is only an approximation (although reasonable given the parameter values), and the presence of this approximation might be noted. In fact, the action of drug can alter the proportion between proliferating and quiescent cells which is characteristic of the pre-treatment balanced exponential growth, so influencing the age distribution if $\gamma>0$.

9. Appendix 2. It would be useful to report the mathematical equations that express Td, GF and Tpot in terms of the model parameters Tc, $\theta$, $\mu$, $\gamma$, in order to clarify how $\theta$ and $\mu$ can be found from Td, Tc, GF and $\gamma$, and how the constraint on Tpot works.

What next?: Accept after minor essential revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

I declare that I have no competing interests