Author's response to reviews

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

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Cell killing and resistance in pre-operative breast cancer chemotherapy

Paolo Ubezio and David Cameron

Dear Sir,

Thank you for forwarding us the helpful comments of the reviewers. The paper was revised according to the suggestions of the referees. Detailed answers to the referee’s requests are reported below. The style of the paper was also revised in compliance with editorial policies.

Thanking the referees for their constructive criticism, we hope that you find this Revised Version acceptable for publication in BMC Cancer.

In the meantime, I would like to send you my best wishes and regards.

Sincerely yours,

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Responses to reviewers

Responses to: Zeljko Bajzer

Major compulsory revisions

1) The derivation of the model equations from the age-dependent theory has been explicitly included in detail in Appendix 1, which has been extensively re-written in the revised version. The link between the age-dependent underlying theory and the age-independent difference equations is provided by the definition of the parameter “u”. This issue was explained and commented in the new Appendix 1. The age dependent theory allows to take into consideration the available information (from literature or by direct individualized measures) on Td, Tpot and GF, linking these quantities to the parameters of the difference equations used in the simulation of tumor growth.

2) Parameters µ and θ are not independent. They depend on Td, Tc (or Tpot), GF and γ, as explicitly stated in the revised version (page 7: “The other parameters (θ and µq) are dependent on these four quantities.”). These relationships follow from the Bertuzzi-Gandolfi theory with some calculations, reported in the revised Appendix 2.

3) We used Gaussian distribution of data errors. The sentence (page 8) was changed in this way: “...maximising the likelihood function of the logs of tumour volumes, with Gaussian distribution of data errors, taking their standard deviation as a parameter.”

Minor Essential revisions

1) The unit was added (0.1 cm$^3$).

2) The sentence was rewritten (page 4) as follows: “an essential feature in the new model is the consideration of quiescence, together with proliferation and cell loss, exploiting the results of the mathematical theory of age-structured cell populations with a quiescent compartment. As a consequence, the response to treatment was modelled taking into account of the different effects against cycling and quiescent cells.”

3) Done (page 9).

Discretionary revisions

1) New references have been included in the revised version (page 3).

2) New references have been included in the revised version (page 4).

3) We adopted the dot for multiplication.

4) This issue was included in the revised appendix 1.
Responses to: Alberto Gandolfi

Minor essential revisions

1) The sentence was corrected as requested (page 7).

2) The use of \( z ( \approx \Delta) \) instead of \( \Delta \) was explained in the Appendix 1 in the revised version. It is a refinement of the equation to make the theoretical and simulated \( T_d \) to be the same value. Appendix 1 was re-written in order to make explicit the derivation of the equations.

3) Done (Appendix 1).

4) Table 1 was corrected in the revised version.

Discretionary Revisions

5) The average and standard deviation of %ki67+ were included. (page 6)

6) The values of \( k \) have been included in the legend for the examples shown in figure 1.

7) The time of the switch has been included in the revised version (page 11)

8) This issue is now discussed in the appendix 1 of the revised version.

9) The formulae were included in Appendix 2.