Analysis of in vivo responses by mixed-effect models reference
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Objectives. In in vivo experimentation, the large intra-group variability between animals is a major obstacle that prevents to detect significant therapeutic effects of treatment factors. Our objective is to assess a new statistical method able to better estimate and characterize the additive effects of the combination of an oncolytic virus (TG6002) and the prodrug flucytosine (5-FC) associated in an anti-cancer treatment. The experimental data are kinetics of tumor growth collected during in vivo assays carried out on mice.

Method

The experimental set up is decomposed into 4 main steps:

1. a full factorial design of experiments is proposed. TG6002 was tested at four concentrations in combination or not with 5-FC. Eight groups of 13 mice are randomly affected to each experimental condition.

2. we propose a mixed-effect model to describe the kinetic growth of the mean tumor diameter.

3. the model parameters are determined with a maximum likelihood estimator based on an expectation-maximization algorithm.

4. effects of the two examined components are assessed with a Wald test.

Results

Our model structure fits correctly all the 104 observed growth responses. The confidence on the estimation results is such that we can detect two treatment effects. Indeed, we show a 3% reduction of the therapeutic response time due to 5-FC and a division by five of the growth delay with TG6002.

Conclusion

Results confirm the relevance of mixed-effect kinetic models to increase the power of statistical tests applied to in vivo studies and efficacy of the combination TG6002 with 5-FC.

Reference


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