A mixed-effect modeling framework to personalize treatment of low-grade glioma patients

Pauline MAZZOCCO, Inria Sophia Antipolis-Méditerranée

Benjamin RIBBA, Inria Sophia Antipolis-Méditerranée

Objectives: Low-grade gliomas (LGGs) are slow growing brain tumors associated with patient survival up to 20 years. Temozolomide (TMZ) is an oral molecule widely used to treat LGG patients. The treatment is usually given the five first days of each month (which constitutes one cycle), for 12 up to 30 cycles. One of the burning questions regarding the management of LGGs is how long a patient should be treated. The objective of the study is to develop a mixed-effect modeling framework to predict the duration and the effect of the treatment according to patient personal information - including genetic statuses and early tumor size observations in order to optimize the duration of TMZ treatment.

Method: Our dataset contains 77 patients for a total of 952 tumor diameter observations manually segmented on MRIs, representing 12 observations per patient on average (4 observations at minimum, 28 at maximum) [1]. The median follow-up duration is 21 months (5 months at minimum, 9.5 years at maximum). Among the 77 patients, 45 (58%) experienced tumor progression and 28 patients (36%) had progression during treatment. The progression time was 14.3 months in median (4.6 months at minimum, 7.5 years at maximum) from treatment onset. We propose a Tumor Growth Inhibition mixed-effect model to describe the observed tumor diameter dynamics accounting for possible tumor progression during treatment. Driven by plausible biological assumptions, the model is formulated as a system of ODEs distinguishing between two cell populations both sensitive to TMZ [2]. The 9 population parameters of the model are estimated with the SAEM algorithm implemented in Monolix (Lixoft). Genetic statuses (p53 mutation and 1p19q codeletion) are included as covariates. Simulations of the population model with covariates are used to investigate the benefit of prolonging TMZ treatment with respect to patients genetic statuses.

We then use early tumor size measurements and genetic statuses to further investigate the ability of the model to predict, at the individual level, two clinically-relevant tumor size metrics: the time to tumor growth (TTG) which is the duration of tumor size decrease until regrowth (progression) and the minimal tumor size (MTS) which characterizes the amplitude of the response. To do so, for each patient, we only consider observations before the 3rd month of treatment to compute the empirical Bayes estimates (EBE) of the individual parameters. EBEs are calculated with a MAP (Maximum A Posteriori) algorithm, using the population parameters previously estimated as prior distributions. EBEs are then used to simulate the model and to compute the two metrics for the 45 patients with observed progression.

Results: Our results indicate that knowing whether a LGG patient is p53-mutated or not is the first important step to personalize his/her therapy. Indeed 18 cycles appears to be a maximum for p53-mutated patients beyond what the benefit in term of tumor reduction is minor with important risk of tumor progression during treatment.

Moreover extracting information through the MAP algorithm only based on tumor size observations before the 3rd month of treatment seems sufficient to correctly predict the amplitude of response for 85% of patients and its duration for 2 years.

To improve the prediction capability of the model, we recommend that clinicians perform, when possible, two MRIs for tumor size measurements before the 3rd month of treatment.

As a perspective, this modeling framework could be used by clinicians to personalize on an individual basis the duration of TMZ treatment in LGG patients.

Références

[1] Ricard D, Kaloshi G, Amiel-Benouaich A, et al., *Dynamic history of low-grade gliomas before and after temozolomide treatment.*, Ann Neurol, 2007.

[2] Ribba B, Kaloshi G, Peyre M, et al., *A Tumor Growth Inhibition Model For Low-Grade Glioma Treated With Chemotherapy or Radiotherapy.*, Clin Cancer Res, 2012.

Pauline MAZZOCCO, 2004 route des Lucioles 06902 Sophia Antipolis Cedex - France
pauline.mazzocco@inria.fr