Nonlinear joint models for drug development

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Résumé

Nonlinear joint models capture the association between one or more biomarkers of interest and a clinical endpoint.

These models can support drug development, notably in oncology where longitudinal measurements of tumour size and/or serum biomarkers are collected throughout the clinical studies although the final evaluation only relies on a time-to progression or overall survival analysis.

To support this claim, I will first present a joint model-based approach to earlier estimate the hasard ratio of a phase III clinical trial within the interim analysis context.

This approach proved more powerful than a Cox model in a simulation study but the performance of the joint model-based approach is sensible to model misspecification as illustrated in a retrospective analysis of the phase III clinical trial ICARIA.

Second, I will present a Bayesian framework where a priori distributions from animal studies are used to fit a joint model to longitudinal tumour size and survival data collected in the Sorafenib arm of an international, randomized, open-label Phase III clinical trial in advanced hepatocellular carcinoma. These informative a priori distributions proved capable of stabilizing the estimation process and reducing the number of patients needed to quantify the association between the sorafenib threshold concentration for tumour eradication and overall survival.

Finally, I will present a meta-regression on the association coefficient estimates from the nonlinear joint models of tumour size trajectories and overall survival in the atezolizumab based treatment arm of 10 clinical trials. This last work reinforces the idea that the tumour growth rate under treatment can help describe the overall survival, although with various strength across studies and cancer types.

These works advocate for a more systematic use of nonlinear joint models in therapeutic drug evaluation, from the early to late phases.

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