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Pemetrexed-Cisplatin

Small Cell Cancer in Response to Administration of Bevacizumab and Modeling Primary Tumor Dynamics of Human-to-Mouse Xenografted Non-Small Cell Lung Cancer.

Methods

• Experiment: Data comes from previous experiment [2] where 77 mice were randomized into 5 treatment groups:
  i) control (saline; N=15),
  ii) beva then pemetrexed-cisplatin after 3 days
  iii) beva then pemetrexed-cisplatin after 8 days
  iv) concomitant beva + pemetrexed-cisplatin
  v) pemetrexed cisplatin alone

• Statistical Analysis: Tumor size was evaluated by fluorescence and the resulting data were analyzed using the stochastic approximation expectation maximization algorithm implemented in Monolix 2018 R1. Standard model diagnostics were completed using various R packages as well as other components of the Monolix Suite.

Results

In Figure 2, the underlying structural model is depicted. Bevacizumab and the chemotherapeutics are both delayed by parameters \( \tau_\alpha \) and \( \tau_\kappa \), respectively before exerting their various effects. The chemotherapeutics inhibit the growth of the tumor while Bevacizumab enhances the action of the chemotherapeutics by transiently increasing vascular quality. The Tumor volume grows at a generalized logistic rate parameterized by \( \alpha \), \( \kappa \), and \( \nu \). The death of the cells damaged by the cytotoxics is modeled via two cell death compartments parameterized by coefficient \( K \).

In Figures 3 through 7 the resulting fit of the model vs the observations for the various treatments on log-10 scale. The vertical error bars are the 50%-IQR on the predictions the model provides (Monte-Carlo approximation expectation maximization algorithm) implemented in Monolix 2018 R1. Standard model diagnostics were completed using various R packages as well as other components of the Monolix Suite.

Conclusions and Perspectives

• Our model-based analysis showed that a revisited Logistic (Gompertzian) growth function was predictive for modeling the effect of various scheduling of pemetrexed-cisplatin and bevacizumab in NSCLC tumor carrying mice. The model will further be refined and then used to anticipate the optimal delay between anti-angiogenesis therapy and chemotherapy, and its dependence on the therapeutic dosing schedule.

• Structural identifiability of the model parameters was further confirmed using sensitivity analyses; the estimated correlation of the random effects (<0.10 for most parameters) and the accurate precision of the final model parameters (RSE<20%). To get this low RSE, some parameters such as \( \nu \) were fixed to reasonable values. The validity of final model parameter estimates was further confirmed through visual predictive checks using 1000 Monte-Carlo simulations although before publication the numerical value of the estimates will be precisely analyzed.

References