Joint longitudinal ordered categorical model for drug-induced diarrhea and colitis: a case example in oncology

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Objectives: Serious diarrhea and colitis adverse events (AEs) are commonly encountered toxicities impacting cancer chemotherapy, molecular targeted agents, and/or cancer immunotherapy. The objective of this work is to illustrate the application of a joint longitudinal ordered categorical model to quantitatively assess the occurrence of diarrhea and colitis and the exposure-safety relationship to support early clinical development in oncology.

Methods: A joint longitudinal ordered categorical model with first order Markov chain was developed based on diarrhea and colitis grade data from 357 patients received an oncology compound in phase I/II trials. Exposure-response was investigated using kinetic-pharmacodynamic (KPD) model. A two-compartment catenary model was used to explain the delay between the occurrences of two AEs.

Results: Both AEs showed positive exposure-response relationship based on exploratory graphical analysis, with lesser extent for colitis. Because of limited occurrences, grade 1 (32%), ≥2 (27%) for diarrhea and grade ≥2 (7%) for colitis were modeled. The joint model successfully captured the data for both AEs, and was qualified by posterior predictive check for the proportion of AE grade over time. The KPD model described the gradual accumulation of exposure (dose) driving the diarrhea events, with half-life ~60 days. An extra compartment (with same half-life) was needed for colitis given the further delayed occurrence. A correlation coefficient of 0.6 between patient-level random effects for the two events was estimated. Anti-diarrhea co-medication (steroid) was also significant in the model.

Conclusions: The longitudinal ordered categorical modeling has been increasingly used for safety endpoints to inform dose/regimen selection. This work exemplifies its application for diarrhea and colitis, which are common toxicities for many anti-cancer agents. The joint model can be a good approach to explore the dependence of such mechanistically correlated AEs. Medical interventions must also be considered in the analysis as it impacts AE grade and duration.

References