Pharmacometric modelling of adverse drug events during anti-cancer treatment

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Introduction: Adverse drug events (ADEs) are common in anticancer therapies. They are burdensome for patients, may lead to discontinuation of treatment and compromise therapeutic outcomes. The patient's perspective can be considered through the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) [1]. Predicting PRO-CTCAE may enable more targeted and individualized therapeutic and supportive intervention.

Aim: This work aims to develop pharmacometric models describing the time course of severity of PRO-CTCAE symptoms and to identify relevant covariates affecting symptom burden.

Methods: Minimal continuous-time Markov models (mCTMMs) are suitable to modeling categorical outcomes, such as PRO-CTCAEs, in real-world data, as they can estimate precise parameters even with limited data [2]. Data from two prospective observational studies were used to develop mCTMMs. Patients were treated with fluorouracil, axitinib, or cabozantinib and completed PRO-CTCAE questionnaires to report selected ADEs. The follow-up period ranged from 12 weeks to three years. Additional information, e.g. plasma concentrations, was collected. MCTMMs were developed for each symptom-drug combination. Pharmacokinetic parameters, such as clearance (CL) and area under the curve (AUC), were estimated and tested as covariates. Covariates were included in the model structure if they led to a significant reduction in the objective function value (p-value < 0.01).

Results: 80 patients were enrolled in the studies. 750 PRO-CTCAE questionnaires were collected. For some symptoms, significant covariate effects were identified. The mCTMM for hand–foot syndrome showed that patients treated with axitinib were less likely to transition between severity grades, remaining at the same grade for longer periods. The probability of experiencing severity grades ≥ 1 was lower with axitinib than with cabozantinib. Covariate analysis showed that including CL improved parameter precision.

Conclusion: This was the first time that Markov models had been developed to predict PRO-CTCAEs. It was demonstrated that this approach is feasible and could be a promising approach for directly accounting for ADEs in precision dosing. Model performance was improved by the inclusion of covariates, such as CL, revealing relationships between exposure and the development of ADEs. Including biomarkers as covariates could provide further insights into patient-specific ADE progression.

Literature:

[1] Minasian LM et al. Patient Relat Outcome Meas, 2022, 13, 249-258
[2] Schindler E et al. AAPS J, 2017, 19, 1424-1435

Short CV:

Nadja Haas completed her studies in Pharmacy at the University of Bonn and joined the research group of Prof. Ulrich Jaehde in 2021 to pursue her Master's degree in Clinical Pharmacy. As a PhD candidate within the same working group, she focuses on the prediction of adverse drug reactions during anti-cancer therapy. By applying Markov models, her work aims to account for adverse reactions in model-informed precision dosing, thereby improving therapeutic outcomes and patient safety. In the ongoing ON-TARGET study, she was able to demonstrate the influence of drug exposure of patient-reported hand-foot syndrome. She attended the Uppsala Pharmacometric Summer School, where she showcased her work and engaged in scientific discussions. Her research has been presented at several scientific conferences, including an oral presentation at the annual meeting of the Deutsche Pharmazeutische Gesellschaft and a poster presentation at the Population Approach Group Europe meeting in 2025.