Optimal Design of Anticancer Regimens
Camille Vong*, Lena E. Friberg, Mats O. Karlsson and Andrew C. Hooker
Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden
*corresponding author: camille.vong@farmbio.uu.se

Background and Objective
Anticancer regimens are often a delicate compromise between dose intensity and acceptable toxicity. One of the rationale is to obtain a better response while limiting adverse effect, for example neutropenia, by avoiding a neutrophil count at nadir to be below grade 4. The aim of the present study was to develop methods in an optimal design approach to select the optimal dosing and sampling strategies within defined restrictions, based on clinical endpoints such as predictions of nadir neutrophil counts for a commonly used anticancer drug docetaxel.

Methodology
PKPD model:
Concentration-time profiles of docetaxel were predicted using typical population PK parameters [1] in patients treated with 1-hour infusion total dose of 100 mg/m² during one cycle of 21 days. A semi-mechanistic model of myelosuppression [2-3] was used to describe the neutrophil time-course for a very rich sampling design and to determine the population nadir value of Absolute Neutrophil Count (ANC) and the time of nadir.

Optimization setup:
A user-defined penalty function implemented for each of the following designs was performed in PopED v.2.21.4 [4] to optimize on both time and size of dosing. Constraints investigated included 1) 5 doses of 20 mg/m² given within 21 days (optimization on a dosing interval), 2) 5 doses of 20 mg/m² given within 21 days (optimization on different dose times), 3) 5 doses given every 5 days starting on day 1 with a total dose of at least 100 mg/m² (optimization on dose size) 4) 5 doses given within 21 days starting on day 1 with a total dose of at least 100 mg/m² (optimization on dose size and dose times). The investigated optimality criterion was to maximize the expected mean nadir value (Eq. 1).

Results

Fig 1: PKPD model for docetaxel with linear drug effect Edrug

Fig 2: Response curves, dosing schedules and proportion of patients experiencing each toxicity grade per design based on 4 different sets of design constraints

Fig 3: Comparison between sampling schedules and Relative Estimation Errors (REE) for nadir value and time to nadir precision after one cycle of treatment.

References