# Optimal Design of Anticancer Regimens

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## 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.

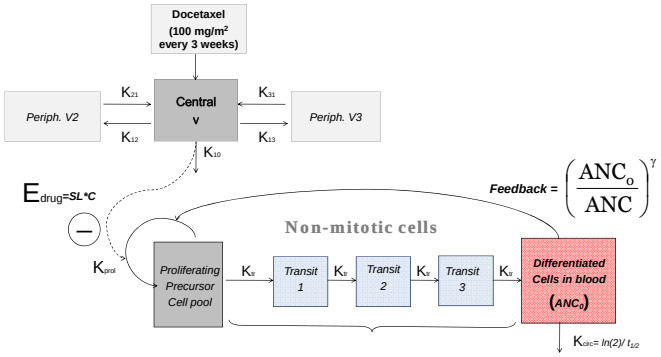


**Fig 1: PKPD model for docetaxel with linear drug effect Edrug**

The PK model is a three-compartment model with a first-order of elimination. The PD model consists of one compartment representing the proliferating cell pool, three transit compartments with maturating cells and one compartment of circulating observed neutrophils. MTT is the mean transit time though the chain, $K_{tr}$ proliferation rate constant, $K_{circ}$ elimination rate constant for circulating neutrophils, $E_{drug}$ drug effect and Feedback representing the feedback loop from circulating neutrophils. $t_{1/2}$= 7 hours.

**Optimization setup:**

- **Dosing schedule**

A user-defined penalty function implemented for each of the following designs was performed in PopED v.2.11[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).

Comparison in terms of proportion of patients experiencing each toxicity grade was performed with a basic design evaluated at [0 7 14 21 42] days after a single 1-hour infusion dose of 100mg/m².

- **Sampling schedule**

Sampling schedules constrained to 7 sampling times to be distributed within 42 days for 1 treatment cycle of 1-hour infusion dose of 100mg/m² were also optimized to allow for model identification of the nadir using:

- C-optimal criterion [5] for better precision in the predicted nadir value (Eq. 2)
- Sample Reuse Simulation approach (SRS) [6] for better precision in measured nadir value –i.e. more accurately reflecting the true nadir (Eq. 3)

Comparison was performed with the basic design and a D-optimal design on sampling times. Relative Estimation Error (REE) computations for nadir value and time to nadir were obtained from multiple simulations and re-estimations.

$$\text{argmax}\left|\min\left\{f(\vec{\theta},\vec{\eta}_i,\vec{a}_i),\vec{\varepsilon}_i\right\}\right|_{\vec{\eta}_i=0,\vec{\varepsilon}_i=0} \quad \text{(Eq. 1)}$$

$$\text{var}\left\{\hat{f}(\hat{\theta})\right\} = c^T\{FIM\}^{-1}c \quad \text{with} \quad c = \left\{\frac{\partial f(\vec{\theta})}{\partial\theta_1}\ \frac{\partial f(\vec{\theta})}{\partial\theta_2}\ \ldots\ \frac{\partial f(\vec{\theta})}{\partial\theta_n}\right\}\Bigg|_{\theta=\theta_0} \quad \text{(Eq. 2)}$$

$$\text{argmin}\left|N^{-1}\sum_{i=1}^{N}\left\{\hat{T}_{nadir}(t_i,\vec{\eta}_i,\varepsilon_i) - T_{nadir}(t_i,\vec{\eta}_i,\varepsilon_i)\right\}^2\right|_{\vec{\eta}_i=0,\vec{\varepsilon}_i=0} \quad \text{with N=number of simulations} \quad \text{(Eq. 3)}$$

θ = parameter  η = inter-individual variability  ε = residual error  a=covariates/doses  $T_{nadir}$ = estimated  $\hat{T}_{nadir}$= predicted

## Conclusion

Optimal design methodology could be applied for different optimality criteria such as toxicity monitoring within oncology studies constraints. Designs resulting from these approaches differ from the ones performed with the classical approach of optimizing parameter precisions and could be more informative to specific clinical endpoints. Future optimal dosing designs will incorporate both efficacy and toxicity defined in a futility function and incorporate between subject variability.

## Results

**Optimized dosing schedule:**

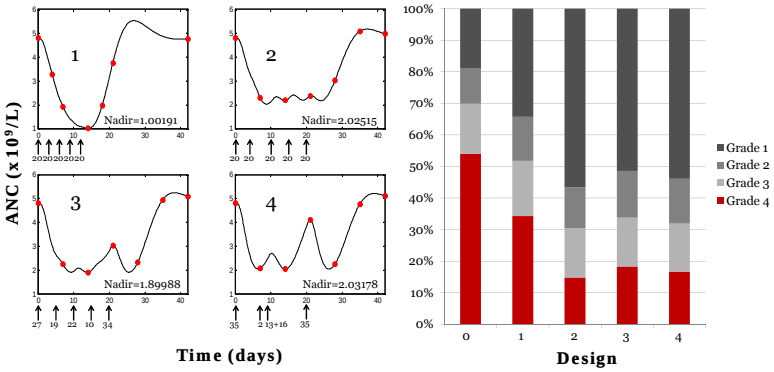


**Fig 2: Response curves, dosing schedules and proportion of patients experiencing each toxicity grade per design based on 4 different sets of design constraints**

Typical population nadir values were extracted from 1000 simulations based on each dosing regimen and reported in each respective toxicity grade. Design 0 represents the original single dose of 100 mg/m² , design 1-4 represent the 5 doses optimized designs based on the optimality criterion of a maximum expected nadir value .

**Optimized sampling schedule:**

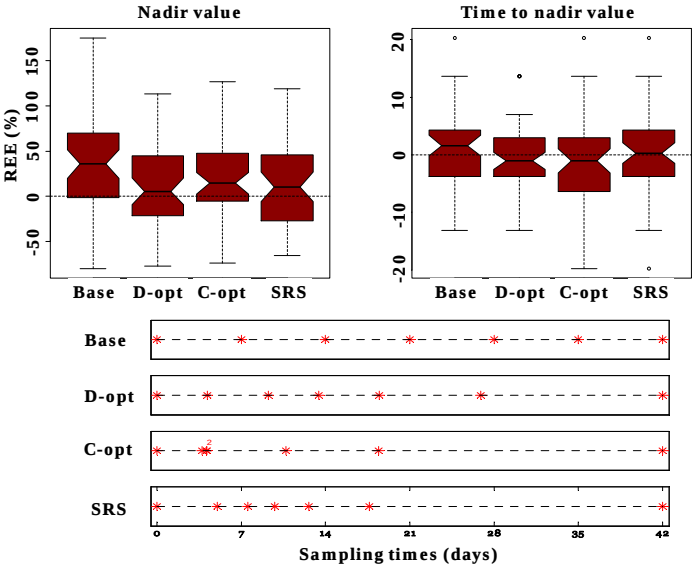


**Fig 3: Comparison between sampling schedules and Relative Estimation Errors (REE) for nadir value and time to nadir precision after one cycle of treatment.**

Upper left panel: REE for the nadir value for the 4 designs. Upper right panel: REE for the time to nadir value for the 4 designs. The boxplot represents the median (middle bar) and the interquartile range (box limits), with points for the outliers. Lower panel: sampling points over 42 days experimental duration for the 4 designs. Raised numbers indicate multiple of sample.

## References

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