

Title: Schedule Dependence in Tumor Response for 5-Fluorouracil in Colorectal Cancer

Authors: Lena E. Friberg*, Mats O. Karlsson

Institution: (1)Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Objectives: Despite numerous clinical studies of different schedules of 5-fluorouracil (5-FU) in colorectal cancer the administration schedule that maximizes tumor response is unknown. A much higher total dose of 5-FU is tolerated when administered as an infusion over several days compared to when administered as an injection. This is because 5-FU shows non-linear pharmacokinetics due to capacity-limited elimination and because dose-limiting toxicities are schedule dependent. The aim of the present study was to create a pharmacokinetic-pharmacodynamic (PKPD) model for the response rate (RR) in colorectal cancer following 5-FU administration and to evaluate if RR is dependent on administration schedule when the non-linear pharmacokinetics is considered.

Methods: A review article [1] reported the response rates in 31 studies where different schedules of 5-FU had been administered alone in metastatic colorectal cancer (Table 1). The observed response rates (partial + complete responses) in 39 study arms were modeled in NONMEM. The concentration-time profiles for each reported schedule were predicted for a typical patient using a population PK model with capacity-limited elimination for 5-FU [2].

A general model [3] was applied to characterize the concentration-response relationship. In this model the concentration exert a direct effect (E_{dir}) described by a sigmoid Emax-model or a simplification thereof (Fig. 1). The area under the curve for the direct effect vs. time ($AUCE_{dir}$) is related to the observed effect (E_{obs} ; here RR) by a second sigmoid Emax-model (or a simpler model). A linear concentration- E_{dir} relationship implies that E_{obs} is independent on the administration schedule (AUC-dependence). A step-function for the concentration- E_{dir} relationship implies that E_{obs} is dependent on the time above a threshold concentration, while Emax-models and sigmoid Emax-models predict relationships in between these two extremes. To compensate for the different cycle lengths of the various study arms, the estimated $AUCE_{dir}$ values were normalized to 4 weeks of treatment. The square root of the number of patients in each study arm was used as weighting factor.

Table 1. 5-FU schedules and their response rates in colorectal cancer taken from Sobrero et al [1]

Type of schedule	Number of study arms	Total dose/ 4 weeks (mg/m ²)	Patients/ study arm (range)	RR (%) (range)
Bolus daily for 5 days every 3 rd -5 th week	13	1850-2500	36-110	1-29
Bolus daily for 3-5 days then once every week	5	1800-3700	19-154	0-33
Bolus once weekly	4	2400-2740	27-72	4-16
Bolus once every other week	3	2400	34-91	12-17
Continuous inf over 1-3 days every to every 3 rd week	5	5200-12000	39-85	0-30
Continuous inf over 5-7 days every 3 rd -4 th week	3	5000-6500	73-88	8-12
Protracted infusion	6	8400	39-87	12-35

Results: The difference in predicted response rates for a linear (AUC-dependent), threshold (time-dependent) and an Emax-model for the concentration- E_{dir} relationship are visualized in Fig. 2 (left panel). In the best model the concentration- E_{dir} relationship was described by an Emax-model with an estimated EC_{50} of 0.613 (RSE 80%) mg/L. The drug-related response rate was linearly dependent on $AUCE_{dir}$ added to a baseline response

$$RR = 10.5\% \text{ (RSE 24\%)} + 0.431 \text{ (RSE 62\%)} * AUCE_{Dir}$$

Consequently, 5-FU was determined to be schedule-dependent in the tumor effect. A prolonged infusion results in a higher response rate and the relative benefit of a continuous infusion increase the larger the total AUC (Fig. 2, right panel).

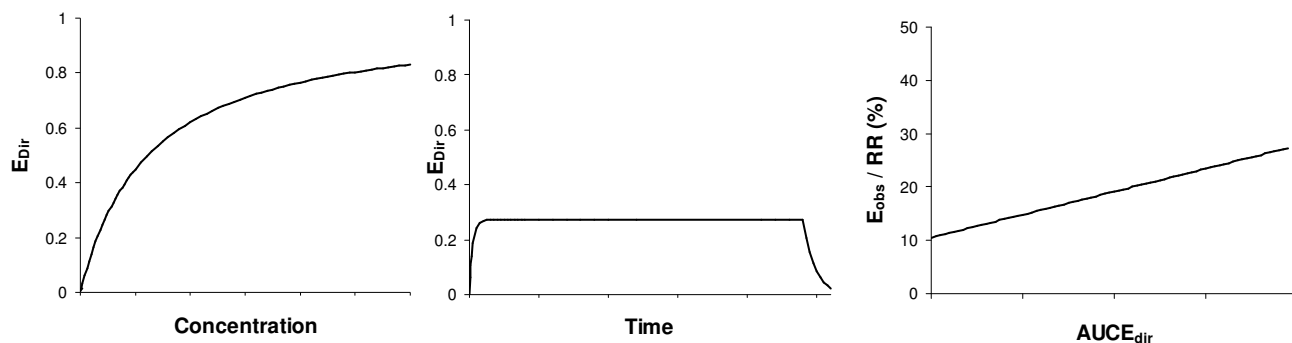


Figure 1. Visual description of the general model [3]. The drug concentration is related to E_{dir} by a sigmoid Emax-model or a simplification thereof (left). If a drug is given as an infusion the resulting E_{dir} over time would be similar to the shape shown in the middle panel. The cumulative direct effect, i.e. the area under the curve for E_{dir} (AUC_{dir}), is related to the observed effect, here exemplified by a linear model (right).

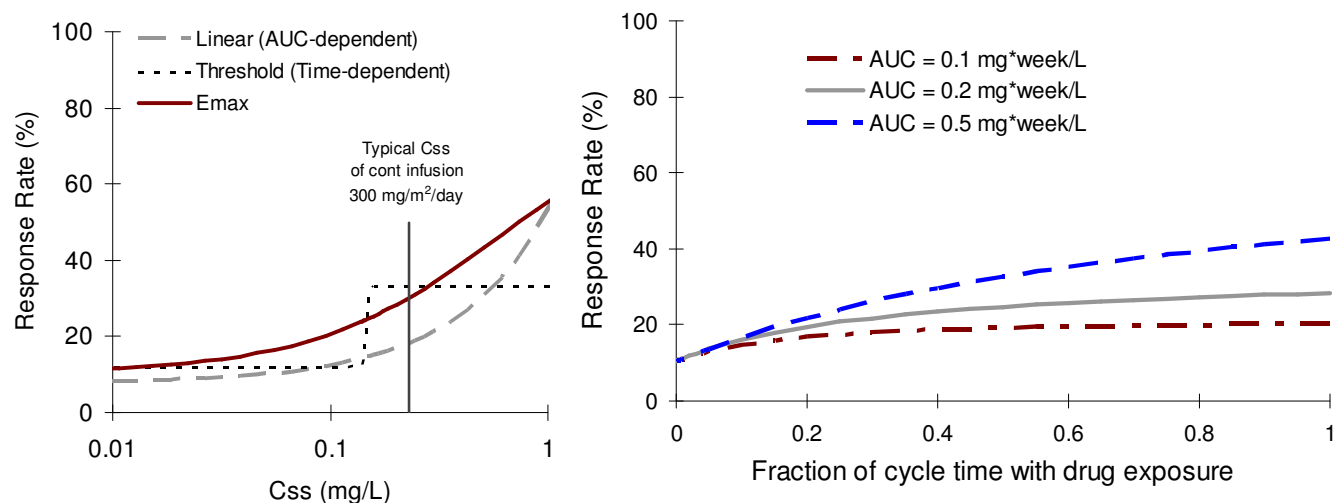


Figure 2. Predicted response rates for three types of models for the concentration – E_{dir} relationship (left) and predicted response rates for the Emax-model following different infusion lengths for the final model in relation to cycle length for different total AUCs (right). A fraction of 1 corresponds to a continuous infusion.

Conclusions: 5-FU is schedule dependent and exerts its highest tumor response rate when administered as a protracted infusion with an increased benefit of a continuous infusion for AUC values >0.1 mg*week/L. The actual AUC tolerated from a protracted infusion schedule is in clinical practice primarily limited by gastrointestinal toxicity and hand-foot syndrome.

References:

- [1] Sobrero AF, Aschele C, Bertino JR. Fluorouracil in colorectal cancer – a tale of two drugs. *J Clin Oncol*, 15: 368-81, 1997.
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