



# Schedule Dependence in Tumor Response for 5-Fluorouracil in Colorectal Cancer

## Background and Objectives:

The administration schedule that maximizes tumor response for 5-fluorouracil (5-FU) in colorectal cancer is unknown.

MTD depends on schedule because 5-FU shows non-linear PK and dose-limiting toxicities are schedule dependent.

The aim was to develop a PKPD model for the response rate (RR) and thereby evaluate if RR in colorectal cancer is dependent on administration schedule of 5-FU when its non-linear PK is considered.

## Methods:

**Data:** Observed RR in 39 study arms of 5-FU schedules in colorectal cancer (Table 1 [1]).

**PK:** The concentration ( $C_p$ ) -time profiles for each reported schedule were predicted using a PK model with capacity-limited elimination [2].

**PD model:** A general model for concentration-effect relationships [3] was applied (Fig 1):

1,  $C_p$  is assumed to exert a direct effect ( $E_{dir}$ ) by a sigmoid  $E_{max}$ -model or a simplification thereof.

If the  $C_p$ - $E_{dir}$  relationship is

**Linear:**  $E_{obs}$  depend on AUC (schedule independent)

**Step-function:**  $E_{obs}$  dependent on time > threshold  $C_p$

**$E_{max}$  or sigmoid  $E_{max}$ :**  $E_{obs}$  depend on relationship in-between extremes above.

2, The area under the curve for the  $E_{dir}$  vs. time curve ( $AUC_{dir}$ ) is related to the observed effect ( $E_{obs}$ ; here RR) by a 2<sup>nd</sup> sigmoid  $E_{max}$ -model (or a simpler model).

**Analysis:** Data was analyzed with NONMEM VI.

$AUC_{dir}$  values were normalized to 4 weeks of treatment to compensate for the different cycle lengths in the studies.

$Sqrt(n_{patients})$  was used as weighting factor.

## Results:

The predicted RR for different  $C_{ss}$  when a linear, a step-function and an  $E_{max}$ -model for the  $C_p$ - $E_{dir}$  relationship were evaluated is visualized in Fig. 2. The  $E_{max}$ -model fit the data the best, indicating that 5-FU has schedule dependent tumor effect but that the relationship can not be simplified to be described by the time above a threshold concentration.

$EC_{50}$  was estimated to 0.613 mg/L (RSE 80%).

RR was linearly dependent on  $AUC_{dir}$  and an estimated baseline response

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

A prolonged infusion results in a higher RR and the relative benefit of a continuous infusion increase with total AUC (Fig. 3).

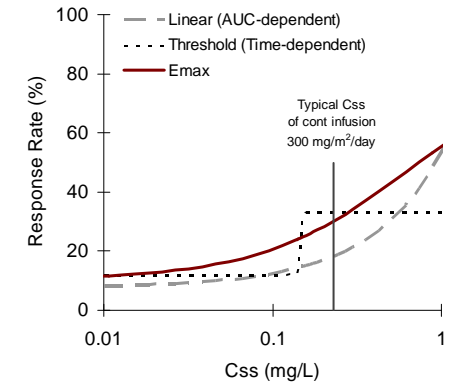


Figure 2. Predicted response rates for three types of models for the  $C_p$ - $E_{dir}$  relationship for different steady-state concentrations of 5-FU.

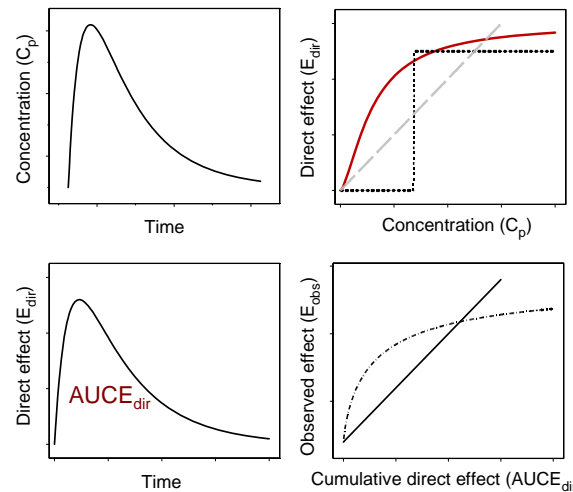


Figure 1. A visual description of the general model [3]. The direct effect is related to  $C_p$  with a linear model (---), a step-function (-.-) or an  $E_{max}$ -model (—). The area under the direct effect vs. time curve ( $AUC_{dir}$ ) determines the observed effect ( $E_{obs}$ ) and is here exemplified with a sigmoid  $E_{max}$ -model (-.-) and a linear model (—).

## Conclusions:

5-FU shows schedule dependent RR in colorectal cancer, also when the non-linear PK is accounted for. 5-FU exerts its highest RR when administered as a protracted infusion.

There is an increasing benefit of a continuous infusion when total AUC increase.

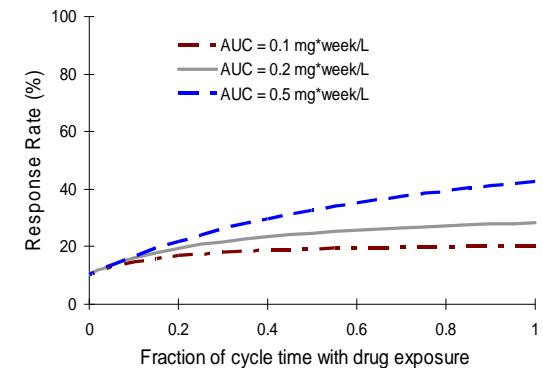


Figure 3. Predicted RR for the  $E_{max}$ -model following different infusion lengths in relation to cycle length for different total AUC values. A fraction of 1 corresponds to a continuous infusion.

Table 1. 5-FU schedules in 39 study arms 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 <sup>2</sup> )	Patients/ study arm (range)	RR (%)
Bolus daily for 5 days every 3 <sup>rd</sup> -5 <sup>th</sup> 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 <sup>rd</sup> week	5	5200-12000	39-85	0-30
Continuous inf over 5-7 days every 3 <sup>rd</sup> -4 <sup>th</sup> week	3	5000-6500	73-88	8-12
Protracted infusion	6	8400	39-87	12-35

## References:

- [1] Sobrero AF, Aschele C, Bertino JR. Fluorouracil in colorectal cancer – a tale of two drugs. J Clin Oncol, 15: 368-81, 1997.
- [2] Sandström M, Freijs A, Larsson R, Nygren P, Fjällskog ML, Bergh J, Karlsson MO. Lack of relationship between systemic exposure for the component drugs of the fluorouracil, epirubicin, and 4-hydroxycyclophosphamide regimen in breast cancer patients. J Clin Oncol, 14:1581-88, 1996.
- [3] Karlsson MO, Molnar V, Bergh J, Freijs A, Larsson R. A general model for time-dissociated pharmacokinetic-pharmacodynamic relationship exemplified by paclitaxel myelosuppression. Clin Pharmacol Ther, 63:11-25, 1998.