The Shape of the Myelosuppression Time-course is Related to the Probability of Developing Neutropenic Fever in Patients with Docetaxel-induced Grade IV Neutropenia

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Background and Objectives

Chemotherapy-induced neutropenic episodes are associated with the risk of developing the potentially life-threatening condition febrile neutropenia (FN), defined as fever ≥ 38.3 °C in combination with grade IV neutropenia, i.e. neutrophil count $< 0.5 \times 10^9/L$.

The aim of the present study was:
- To describe the time-course of myelosuppression in patients treated with docetaxel

- To Investigate if the probability of developing FN in patients with grade IV neutropenia is random or dependent on the shape of the predicted myelosuppression time- course and on other proposed risk factors [1].
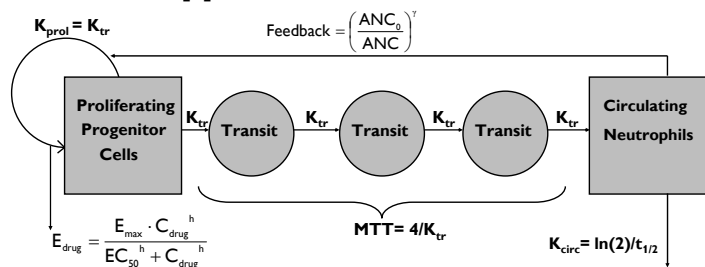

Figure 1. The Semi-physiological model of myelosuppression.
The model consist of one compartment representing the proliferating cell pool, three transit compartments with maturating cells and one compartment of circulating observed neutrophils. MTT is the mean transit time though the chain, K_{tr} proliferation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

Methods

517 neutrophil counts from 140 patients with observed grade IV neutropenia during the first treatment course of a total of 244 breast cancer patients treated with docetaxel (100 mg/m^2) were included in the analysis [2]. 26 of the 140 patients (19 %) experienced FN.

Concentration-time profiles of docetaxel were predicted using typical population PK parameters [3].

A semi-physiological myelosuppression model (Fig. 1) [4] was fitted to the neutrophil observations using the LAPLACE method in NONMEM VI. The neutrophil data were Box-Cox transformed with a factor 0.2 to obtain symmetrically distributed residuals around zero. The half life of neutrophils was fixed to 7 hours.

The myelosuppression model parameters (baseline neutrophil count (ANC_0, mean transit time (MTT) and drug effect parameter EC_{50}), myelosuppression descriptors (nadir and duration of grade IV neutropenia) and proposed risk factors [1] (age, performance status, haemoglobin (Hb) and liver function) were explored to be related to the FN data by logistic regression.

Results

The myelosuppression model could well characterize the neutrophil-time course and resulted in similar system-related parameter estimates as previously observed (Table 1) [4].

The myelosuppression model parameters EC_{50} and MTT were both significantly related to the probability of developing FN (Table 2, Eq.1-3). None of the evaluated risk factors or myelosuppression descriptors were found significant.

$$FN_{EC_{50}} = Slope_{EC_{50}} \cdot \left(\frac{EC_{50}}{TVEC_{50}} \right)^{HILL_{EC_{50}}} \qquad Eq.(1)$$

$$FN_{MTT} = Slope_{MTT} \cdot \left(\frac{MTT}{TVMTT} \right)^{HILL_{MTT}} \qquad Eq.(2)$$

$$PFN = \frac{EXP(FN_{Base} + FN_{MTT} + FN_{EC_{50}})}{1 + EXP(FN_{Base} + FN_{MTT} + FN_{EC_{50}})} \qquad Eq.(3)$$

Eq.(1-3) Logistic regression model for FN. $TVEC_{50}$ (1.39) typical value of EC_{50}; TVMTT (78.3), typical value of MTT; PFN probability of developing FN during the first course of treatment

Table 1. Final population model parameter estimates of the docetaxel semi-physiological myelosuppression model (relative SE %)

Parameter	Estimate	IIV CV %
ANC_0 (x $10^9/L$)	4.7 (1.8)	32 (6.0)
MTT (hours)	78 (1.8)	12 (0.68)
γ	0.16 (2.8)	24 (6.9)
E_{max}	95 (7.4)	-
EC_{50} (mg/L)	1.4 (15)	36 (9.4)
h	1.6 (8.4)	-
Residual error *	0.47 (4.4)	-

ᴷ Additive residual error on Box-Cox scale

Table 2. Final population model parameter estimates of logistic regression model for FN (relative SE %)

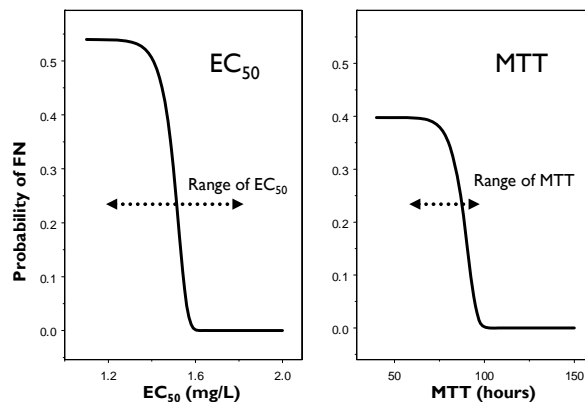| Parameter	Estimate
FN_{Base}	-0.30 (7.9)
$Slope_{EC50}$	-0.11 (2.4)
$Hill_{EC50}$	29 (1.5)
$Slope_{MTT}$	-0.14 (14)
$Hill_{MTT}$	15 (8.4)

Figure 2. The solid curves represent the probability of FN predicted from Eq. (1-3) at various EC_{50} with MTT set to typical value 78.3 (left) and at various MTT with EC_{50} set to typical value 1.39 (right) .

Conclusion

The probability to develop FN is dependent on the myelosuppression time-course. Patients with high drug sensitivity and a fast neutrophil decline have a higher probability to develop FN compared with other patients who experience grade IV neutropenia.

References

[1] Aapro MS., et al., Eur J Cancer; 42:2433-2453, 2006.

[2] O'shaughenssy J et al., J Clin Oncol; 20:2812-2822, 2002

[3] Bruno R., et al., J Pharmacokinet Biopharm; 24:153-72, 1996.

[4] Friberg LE., et al., J Clin Oncol; 20:4713-21, 2002.