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Chemotherapy-induced myelosuppression by Vinorelbine: a comparison between different dose schedules by simulation

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Abstract. – A pharmacokinetic-pharmacodynamic (PK-PD) model was developed to simulate the plasma profile and the toxicity of vinorelbine after multiple oral dose treatment to humans. The PK drug profile was described by a three-compartment open model linked to a PD model aimed to describe the drug toxicity on the circulating neutrophils. Different dose schedules were simulated holding the total administered dose constant (100 mg p.o. during two weeks): 7.7 mg daily (13 doses), 20 mg every 3 days (5 doses) and 33.3 mg every 6 days (3 doses). The lowest values of the circulating neutrophils were observed after 18 days from the start of the treatment and at nadir the fraction of the circulating neutrophils were 0.733, 0.703 and 0.681 after the three doses in decreasing order. These differences were not clinically significant, however the drug bioavailability, which was fixed to 0.35 in the simulation, might be highly variable among subjects contributing to a large extent to the observed variability in drug toxicity.

Key Words:

Vinorelbine, Pharmacokinetics, Pharmacodinamics, Myelosuppression.

Introduction

Vinorelbine (Navelbine, 5'norhydrovinblastine) is a unique semisynthetic analog of vinblastine which differs from other semysinthetic vinca alkaloids in that its structural modifications are on the catharanthine ring instead of the vindoline ring.

Vinorelbine induces cytotoxicity by inhibiting microtubule assembly and has demonstrated significant activity in patients with pretreated breast, non-small-cell-lung, and ovarian carcinomas, as well as lymphoma. Leukopenia was the dose-limiting toxicity of this drug. Vinorelbine pharmacokinetics was extensively investigated in man after both intravenous and oral administration[1-10]. The drug kinetics was linear[8]. After i.v. infusion (30 mg/m^2 in 15 minutes) the plasma concentrations displayed a multiexponential profile and all the parameters of a 3-compartment open model could be estimated[11]. After an oral dose of 80 mg/m^2 (soft-gelatin capsule), vinorelbine was rapidly absorbed (T_{max} = 1.4 ± 0.7 h) and showed a bioavailability of 43 ± 14%.

The pharmacokinetics of vinorelbine was also investigated for 7 days following 70 mg/m^2 orally as a soft-gelatin capsule or 30 mg/m^2 intravenously, and the mean absolute bioavailability of the oral dosage formulation was calculated to be 33% ± 18[6].

A correlation was found between AUC_{last} and nadir variation in white blood cells (WBC) and polymorphonuclears (PMN). More cases of neutropenia (all grades pooled), leucopenia (grades 3-4 only) and nausea (grades 2-3) were induced by 80 mg p.o. than by 25 mg i.v. vinorelbine[4]. A model that can explain and predict both the degree and duration of hematological toxicity after different schedules of antitumoral drugs administration was developed and tested[12], and in the present paper this model is used to simulate and compare the toxicity of vinorelbine after intravenous and multiple oral dose administration to humans.

Methods

The Pharmacokinetic Model

It was assumed a three-compartment open model with a first order absorption to describe

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the kinetics of vinorelbine in the simulation. The compartmental model is shown in Figure 1: q1 (central) is the drug amount in the central compartment, q2 (periph.) is the the drug amount in the rapid equilibrating peripheral compartment, q3 (deep) is the the drug amount in the slowly equilibrating peripheral compartment and q4 (absorp.) is the absorption compartment.

The dose is administered in compartment 1 (i.v. administration) or 4 (oral administration) and in the simulation the oral dose was adjusted according to the drug bioavailability. All the remaining compartments were set to 0 at time 0. The parameters k_{ij} are the transfer constants from comparment j to compartment i. The population estimates of the pharmacokinetic parameters used in the simulation are listed in Table I (V_1 is the volume of the central compartment)[11]. In the same paper were reported also the mean clearance and terminal half-life which were 57 $l \cdot h^{-1}$ and 43 h respectively. The absorption rate constant (k_{14}) was fixed to 0.15 h^{-1} in order to have a peak time close to 2 hours.

The Pharmacodynamic Model

The pharmacodynamic model consisted of one pool that represented stem cells and progenitor cells (i.e., proliferative cells – named prol), three transit compartments with maturing cells (named trans), and one compartment of circulating observed blood cells (named circ). The model is graphicaly shown in Figure 2. A maturation chain with transfer rate constants k_{tr}

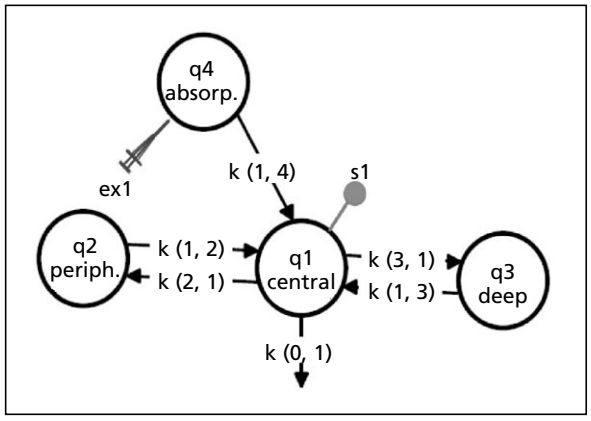

Figure 1. Pharmacokinetic model of vinorelbine in man: ex1 is the drug input in compartment 4 after oral administration (after i.v. administration ex1 is in compartment 1); s1 is the drug concentration in the sampled compartment (i.e., compartment 1).

Table I. Pharmacokinetic parameters (and CV%) of vinorelbine[11].

V_1	21 l	(55%)
k_{01}	3.2 h^{-1}	(29%)
k_{21}	7.7 h^{-1}	(74%)
k_{12}	1.3 h^{-1}	(67%)
k_{31}	4.7 h^{-1}	(53%)
k_{13}	0.04 h^{-1}	(20%)

(compartment 6, 7 and 8) allowed prediction of a time delay between drug administration and the observed effect. The generation of new cells in prol was dependent on the number of cells in the compartment; that is, self-renewal or mitosis, a proliferation rate constant determining the rate of cell division (k_{prol}), and a feedback mechanism from the circulating cells represented by the term $(Circ0/Circ)^{\gamma}$ where Circ0 is the basal level of the circulating cells and Circ is the actual number of circulating cells. The feedback loop was necessary to describe the rebound of cells (i.e., an overshoot compared with the baseline value).

The differential equations were written as:

$$\frac{d\text{Prol}}{dt} = k_{prol} \cdot \text{Prol} \cdot (1 - E_{drug}) \cdot \left(\frac{\text{Circ0}}{\text{Circ}}\right)^{\gamma} - k_{tr} \cdot \text{Prol}$$

$$\frac{d\text{Transit}_1}{dt} = k_{tr} \cdot \text{Prol} - k_{dr} \cdot \text{Transit}_1$$

$$\frac{d\text{Transit}_2}{dt} = k_{tr} \cdot \text{Transit}_1 - k_{dr} \cdot \text{Transit}_2$$

$$\frac{d\text{Transit}_3}{dt} = k_{tr} \cdot \text{Transit}_2 - k_{dr} \cdot \text{Transit}_3$$

$$\frac{d\text{Circ}}{dt} = k_{tr} \cdot \text{Transit}_3 - k_{circ} \cdot \text{Circ}$$

where the variables Prol, Transit_i and Circ are the cell number in the compartments.

The drug amount in the central compartment (q1) was assumed to reduce the proliferation rate or induce cell loss by the function E_{Drug}, which was modeled as a sigmoidal function:

$$E_{Drug} = \frac{E_{max} \cdot q_1^n}{k^n + q_1^n}$$

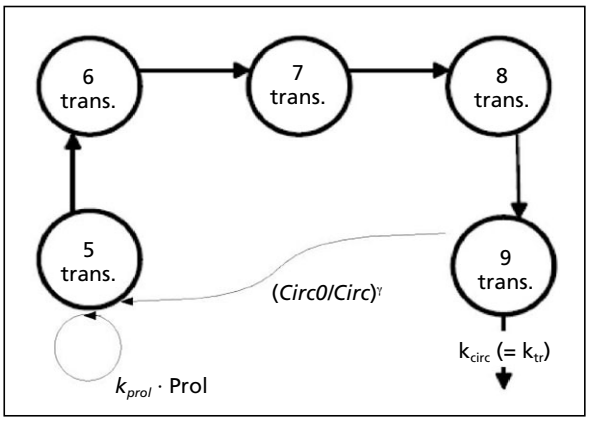

Figure 2. Pharmacodynamic model of vinorelbine in man.

E_{max} was set to 1, which means that when q1 approaches infinity, the drug effect is close to 1 and the proliferating cell production goes to 0, and when q1 is 0 there is no drug effect on the proliferating cells.

In the transit compartments, it is assumed that the only loss of cells is into the next compartment. As the proliferative cells differentiate into more mature cell types, the concentration of the cells is maintained by cell division.

At steady state, dProl/dt = 0, and therefore $k_{prol} = k_{tr}$ and, to minimize the number of parameters to be estimated, it was also assumed that $k_{circ} = k_{tr}$.

To improve interpretability, the mean transit time was estimated, which was defined as MTT = $(n_c+1)/k_{tr}$, where n_c is the number of transit compartments. Thus, the structural model parameters are Circ0, MTT, γ, n and k.

This model has been tested using the data from different antitumoral drugs[12]. The half-lives of circulating cells ($\ln 2/k_{tr}$) were estimated to be in the range 15 to 24 hours and there was no improvement of the fit when the half-life was fixed to a literature value of 6.7 hours. In general, all drugs used to test the model produced similar estimates of MTT and γ, consequently these parameters were fixed in the present simulation to the following values:

$$MTT = 125 \text{ hours}, \gamma = 0.17.$$

Circ0 was also fixed to 1 because this parameter was not of interest in the simulation, consequently Circ may be viewed as the fraction of the circulating cells.

Table II reports the values of all the pharmacodynamic parameters used in the simulation.

The values of k and n were chosen looking at the relationship between the fraction of the circulating neutrophils at nadir and the drug dose. This effect was investigated after single i.v. administration of vinfluvine[13] and the following relationship was assessed between neutrophil count decrease (percent from baseline) at nadir and blood body exposure:

$$y = -0.0028 \cdot x - 26.99$$

were $x = AUC_{infinity}$ in $ng \cdot h \cdot ml^{-1}$ units. Assuming a clearance mean value of $41.4\ l \cdot h^{-1}$, it follows that:

$$AUC = \frac{Dose}{CL} = \frac{Dose}{1000 \cdot 41.1} \ (ng \cdot h \cdot ml^{-1})$$

where Dose is in mg. Substituting this value in the previous equation we get:

$$E_{nadir} = 0.00067 \cdot Dose + 0.27$$

where:

$$E_{nadir} = \frac{Circ0 - Circ_{nadir}}{Circ0} = -\frac{y}{100}$$

In Table III are listed the predicted Enadir and the fraction of circulating neutrophil predicted by this equation in the dose range 10-800 mg.

The vinorelbine effects (Enadir) at the same doses shown in Table III were simulated also using the PK/PD model for different values of k and n (data not shown). Assuming that the toxic

Table II. Parameters of the pharmacodynamic model.

k_{prol}	=	k_{tr}
k_{tr}	=	(nc + 1)/MTT
k_{circ}	=	k_{tr}
Circ0	=	1
E_{max}	=	1
nc	=	4
MTT	=	125 h
γ	=	0.17

Table III. Predicted E(nadir) values for different i.v. doses of vinflunine[13].

Dose (mg)	Enadir	Circ/Circ0 (nadir)
10	0.2767	0.7233
50	0.3035	0.6965
100	0.337	0.663
150	0.3705	0.6295
200	0.404	0.596
800	0.806	0.194

effect of vinorelbine and vinfluvine were comparable, it was concluded by a visual inspection of the simulation results that a reasonable approximation of Circ/Circ0 at nadir may be obtained for k and n close to 0.5 mg and 1 respectively. Then, these values were used in the following simulations.

The Dose Schedules

The simulation was performed to compare the drug effect after the same total dose when given at different dosing intervals. The total dose was fixed to 100 mg p.o. (equivalent to 35 mg of vinorelbine available to the systemic circulation) and the dosing intervals are shown in Table IV.

Results

In Figure 3 are shown the drug profiles after single i.v. (35 mg) and oral (100 mg) administration in the central compartment putting the oral bioavailability to 35%.

In Figures 4 and 5 are shown the drug profiles in the central compartment after multiple oral dose treatment and the corresponding levels of the circulating neutrophils. At nadir the fraction of the circulating neutrophils were 0.733, 0.703 and 0.681 after the 11.7, 7 and 2.7 mg dose treatment respectively.

Table IV. PK/PD simulations: dose schedules.

Dose interval	Number of doses	Dose
1 day	13	7.7 mg
3 days	5	20.0 mg
6 days	3	33.3 mg

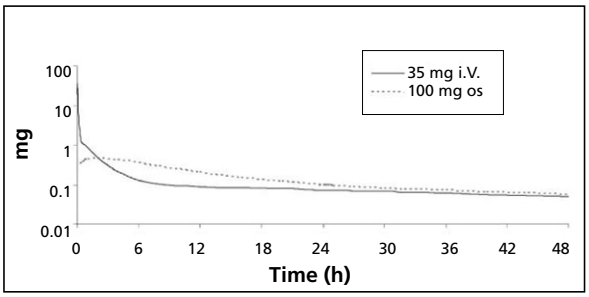

Figure 3. Pharmacokinetics of vinorelbine after single i.v. (35 mg) and oral (100 mg, F = 0.35) administration: drug amount in the central compartment.

Discussion

The PK/PD of vinorelbine was simulated after different dose schedules and the data showed that the toxicity predicted by the model was lower when dose intervals were longer. The circulating neutrophils fraction at nadir were about 0.7 (i.e., 1750 absolute neutrophil count, ANC, assuming a basal value of 2500 ANC) and the predicted differences between the drug schedules were not clinically significant.

According to the international guidelines, neutropenia can be classified in the following classes (ANC measured in cells per microlitre of blood):

- Neutropenia (1500 < ANC < 2000; grade 1) slight risk of infection

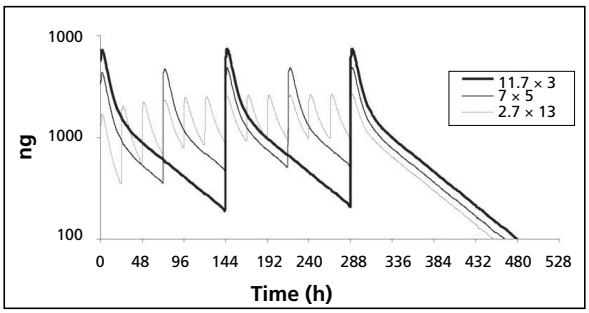

Figure 4. Pharmacokinetics of vinorelbine in the central compartment after multiple oral dose treatment.

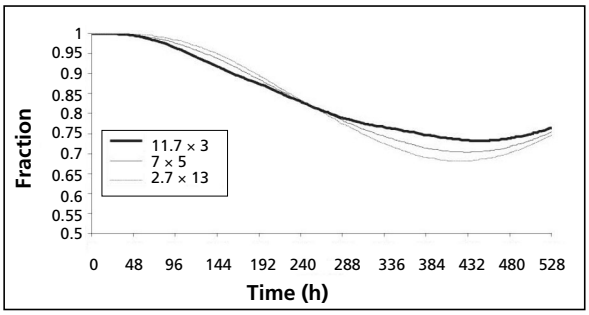

Figure 5. Fraction od the circulating neutrophils after multiple oral dose treatment.

- Mild Neutropenia (1000 < ANC < 1500; grade 2) minimal risk of infection
- Moderate Neutropenia (500 < ANC < 1000; grade 3) moderate risk of infection
- Severe Neutropenia (ANC < 500; grade 4) severe risk of infection

and assuming a basal value around 2500 ANC it can be seen in the simulation that after a total dose of 100 mg p.o. only neotropenia grade 1 can be predicted.

However the low drug bioavailability, which was fixed to 35% in the present simulation, might be highly variable between subjects contributing to a large extent to the drug toxicity variability after multiple dose therapy.

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