Validation of a neutropenia PK/PD model from intravenous vinflunine and its application to design phase I trials with oral vinflunine

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Background and Objectives

Vinflunine (VFL) is a fluorinated microtubule inhibitor with neutropenia as the main dose limiting toxicity [1]. Vinflunine has been first developed as an intravenous form (IV VFL) for cancer therapy followed by an oral form (oral VFL).

Taking the advantage of the oral form and in order to exploit the antiangiogenic effect of tubulin inhibitors, oral VFL is being tested using more frequent administrations and lower flat doses than that used with IV VFL. The objective is to mimic continuous infusion rate which is assumed to result in better tolerability and efficacy [2].

During the early clinical development of IV VFL, a semi-physiological population PK/PD model enabling to describe the time-courses of absolute neutrophil count (ANC) has been developed [3].

The objectives of the study were :

1) To qualify the PK/PD model of IV VFL on different dosing schedules from phase I, II and III data.

2) To use the PK/PD model for simulating haematological toxicity after oral VFL fractioned schedules and to select the best oral dosing regimens

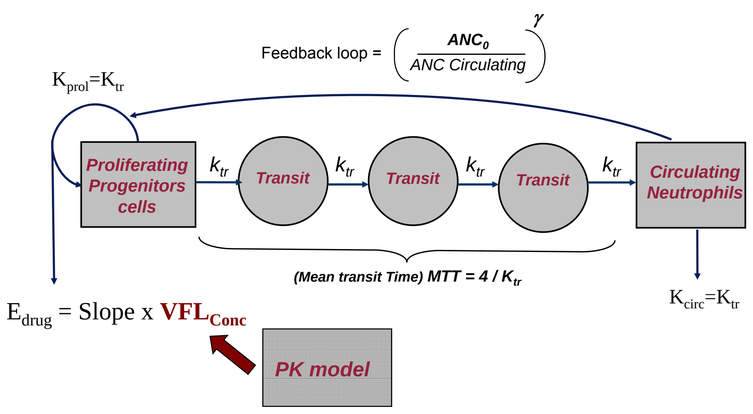

Fig 1 : The PD model is a semi-physiological model of myelosuppression with the system related parameters: Baseline neutrophil count (ANC_0), mean transit time (MTT), feedback factor (γ) and the drug effect Slope. The PK model is a four-compartment PK model with first order elimination and zero order input as infusion rate [4].

Tab1 : Typical population PD model parameters obtained by NONMEM
(FOCE and log-transformed ANC)

	ANC_0 (x 10^9/L)	MTT (h)	γ	Slope (ml/ng)	Proportional error (%)
Estimate (RSE%)	4.55 (4)	123 (3)	0.17 (5)	0.041 (5)	39 (7)
IIV, CV% (RSE%)	46 (13)	-	-	33 (35)	-
IOV, CV% (RSE%)	-	22 (21)	-	31 (48)	-

IIV : inter-individual variability; IOV: inter-occasion variability

Methods

•Qualification of IV VFL PK/PD model:

Internal validation by VPC:

- Observed data from the model building dataset : 1871 ANC values over several treatment courses (432 courses) from 210 patients (single agent phase I and II trials with different schedules of administration).
- Simulated datasets : 300 replicates using typical population parameters of the PK/PD model.

External validation by PPC:

Actual data from a new dataset : 450 patients and 1200 treatment courses from single agent phase II and III clinical trials using once every 3 weeks schedule

Comparison of NCI-CTC grades of ANC between simulated (300 replications) and actual data.

• Model simulation of oral VFL fractioned schedules :

- Oral PK profiles simulated from typical population PK parameters of IV VFL and including preliminary information from a bioavailability pilot study (n=12 patients).
- Time-courses of ANC simulated using different schedules with a same dose intensity (*i.e.* ~ 1000 mg q3 weeks)
- Simulated toxicity profiles (overall incidence, frequency of severe grades, duration of grade ≥ 3) were compared amongst the different designs.

Results: internal validation of IV VFL model : VPC

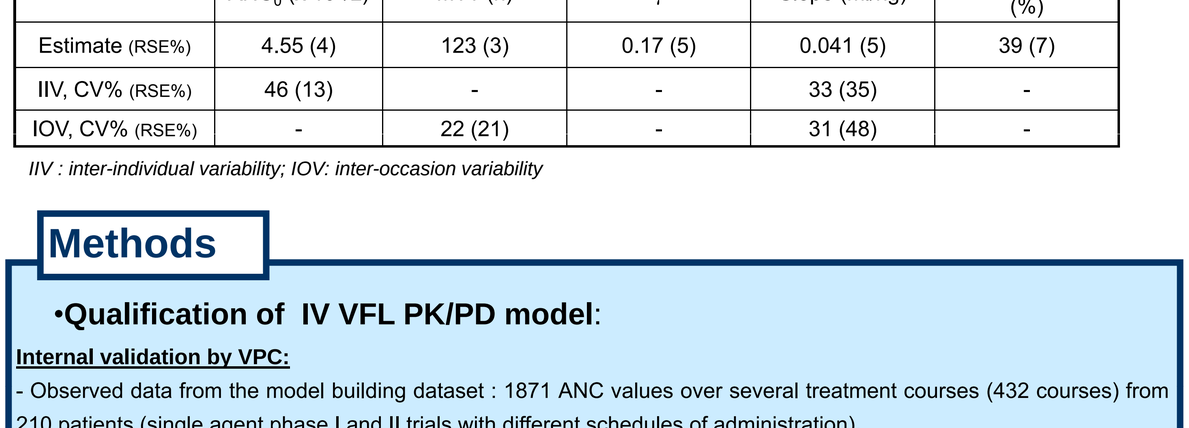

Fig 3: Visual Predictive Check on 3 different schedules (model building data set : 210 patients with PK data). Red triangles are the VFL dosing. Shaded area are the 90% prediction interval of simulated ANC

Neutrophil time-courses after VFL 20 min intravenous infusion were well described on different schedules (once D1 q3W, once D1 & D8 q3W and once weekly) and over repeated courses : see internal-VPC (Fig 3) and external-PPC (Fig 4).

Results: external validation of IV VFL model : PPC

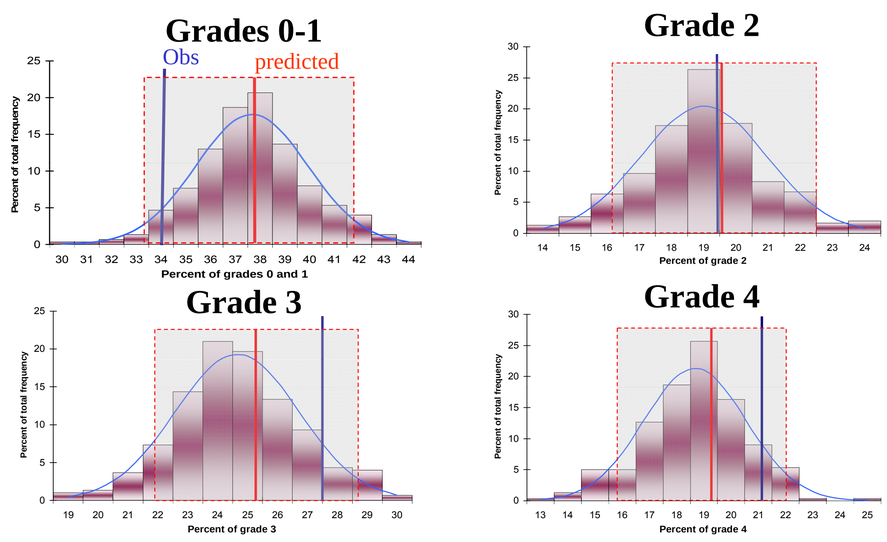

Fig 4: Posterior Predictive Check of the ANC grades on an external dataset – 1st course (424 patients after 250 to 320 mg/m² IV VFL doses once every 3 weeks). PK profiles were simulated from the typical population PK parameters.

Shaded area are the 90% prediction interval of simulated ANC grades and solid red lines are the median of simulations. Blue line is the observed frequency from the original dataset.

Similar results were obtained over the first four courses of treatment (1200 courses).

Results: Simulations of oral VFL fractioned schedules

Tab 2 : Simulation of toxicity profiles (1000 patients) of oral VFL dosing schedules over 3 weeks of treatment

Schedule	Once D1 to D5 q3W	Once D1 to D5 & D8 to D12 q3W	Once D1 to D14 q3W	B.i.d x 2 q1W	Once a day
Oral dose (mg) per administration	200	100	71	83	48
Total dose (mg) over 3 weeks	1000	1000	1000	1000	1000
Neutrophil grades (%) (overall incidence) Grades ≥ 1	89	86	83	77	74
Grades ≥3	**60**	**54**	**52**	**40**	**35**
Grade 4	**31**	**24**	**24**	**15**	**12**
Median ($PI_{90\%}$) duration of grade ≥ 3 (days)	**6 [2 – 13]**	**6 [2 – 14]**	**5 [1 – 12]**	**4 [1 – 13]**	**3 [1 – 12]**

Based on the same dose intensity, better tolerability was associated with dosing regimen having more frequent administrations and shorter doses intervals

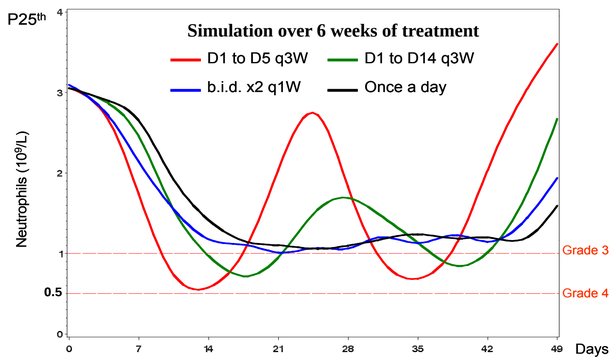

Fig 5: Simulated ANC time-courses after different oral dosing schedules. Each curve represents the 25th percentile from 1000 simulated patients over 6 weeks of treatment.

PK information was generated from the IV VFL typical population parameters, with a bioavailability of 57% (IIV of 20%) and mimicking an oral PK profile by an infusion duration of 2-hours

Conclusions

1) The PK/PD model for neutropenia effect after IV VFL dosing was qualified from both internal and external datasets, and on different schedules.

2) This model together with PK information from a bioavailability pilot study enabled to simulate, to select and to guide new oral VFL flat doses regimen to be tested in clinics.

3) Preliminary results from phase I trials with oral VFL are in line with the simulations (see fig 6).

Examples of individual time-courses of neutrophils from phase I studies with oral VFL

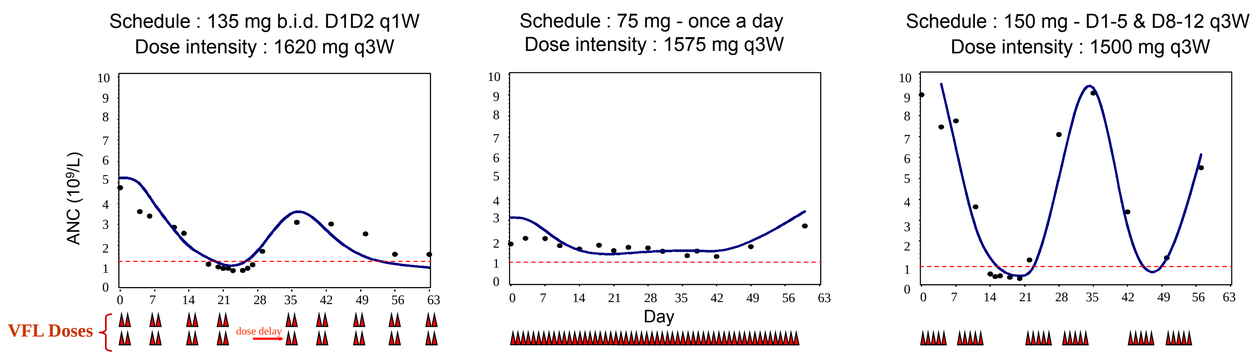

Fig 6 : Individual model predicted (without PK data) and observed ANC in patients after oral VFL administrations

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