

Modeling the dynamics of alanine aminotransferase in advanced cancer patients treated with kahalalide F



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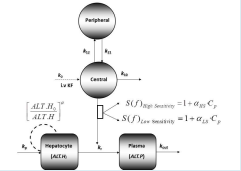
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OBJECTIVES

Kahalalide F (KF) is a cyclic depsipeptide compound belonging to family of kahalalides [1]. Reversible transient elevation of alanine aminotransferase (ALT) is observed after intravenous (iv) administration of kahalalide F (KF) in cancer patients. The aim of this study was to develop a pharmacokinetic-pharmacodynamic model to describe the transient elevation of ALT following different KF dosing schedules.

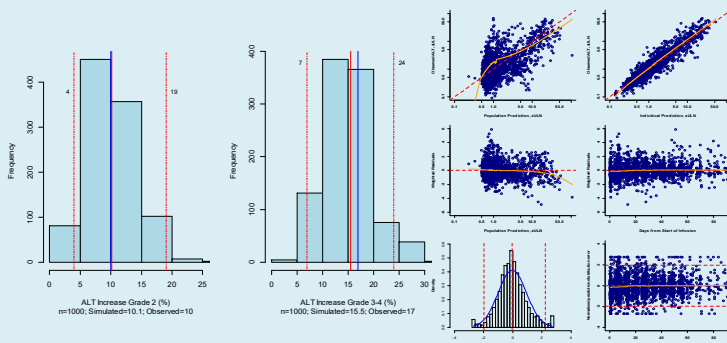
MODEL STRUCTURE

ALT.H₀ – baseline ALT in hepatocyte
ALT.P₀ – baseline ALT in plasma
k_p – ALT production rate in hepatocytes
k_r – ALT release from the hepatocyte into the blood
k_{out} – ALT elimination rate from serum
α_{LS} – slope of the drug effect (low sensitivity)
α_{HS} – slope of the drug effect (high sensitivity)
ϕ – contribution of feedback



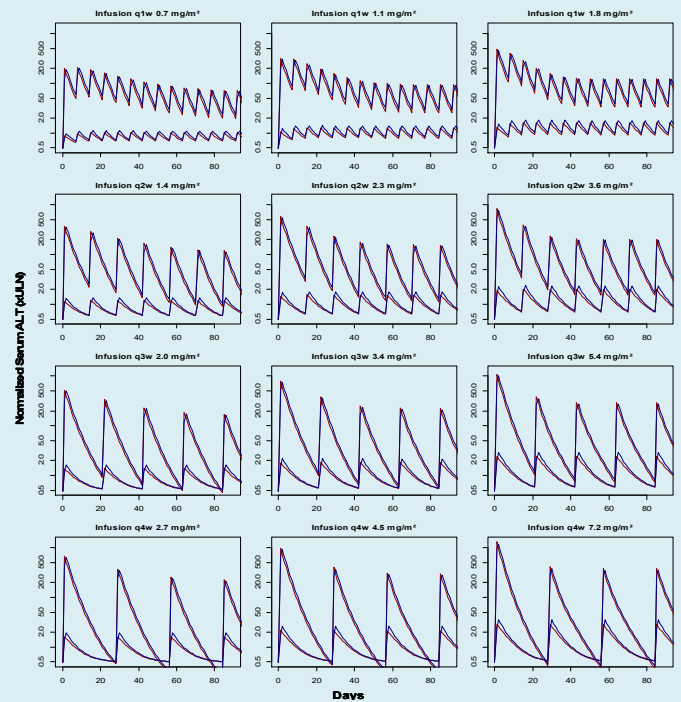
Model diagnostics

Diagnostic results suggested that the semi-mechanistic PD model developed provided a reasonable description of the ALT observations and is adequate to carry out simulations of ALT dynamics.

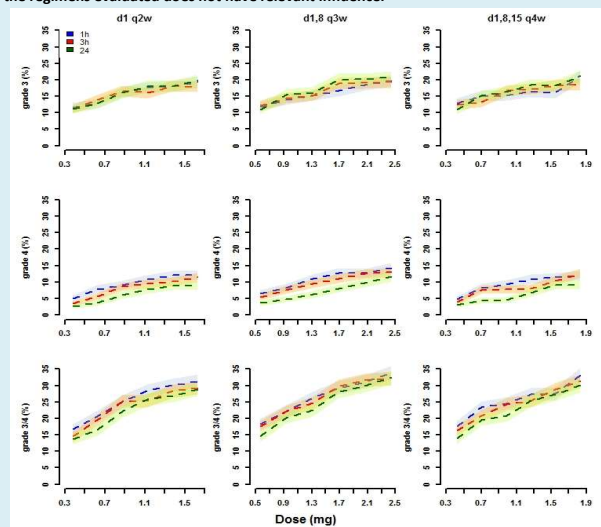


Model-based simulations

Deterministic simulations showed that the effect on ALT elevation is dose-dependent.



Stochastic simulations revealed that KF-induced transient ALT elevation is mainly dependent on the dose infused, whereas the duration of the infusion and dosing frequency employed in the regimens evaluated does not have relevant influence.



Model parameter estimates

The estimates of system-related model parameters were similar to the values reported in the literature, including those reported in a previous population PK/PD model analysis [2].

Parameters (units) – Description	Original Dataset (n=250)	Non-parametric Bootstrap (948 out of 1000 replicates)	
	Estimate (RSE%)	Median (RSE%)	95% CI
ALT.H ₀ (xULN) – baseline ALT in hepatocyte	199 (16.5)	193 (19.1)	114, 291
ALT.P ₀ (xULN) – baseline ALT in plasma	0.517 (4.91)	0.511 (5.52)	0.456, 0.563
Shift (%) – effect of liver metastases on ALT.P ₀	23.9 (41.5)	27.0 (38.9)	7.36, 55.5
k _{out} (h ⁻¹) – ALT elimination rate from serum	0.014 (9.18)	0.014 (9.90)	0.011, 0.017
α _{LS} (mL/ng) – slope of the drug effect (low sensitivity population)	0.477 (11.8)	0.471 (12.6)	0.362, 0.619
α _{HS} (mL/ng) – slope of the drug effect (high sensitivity population)	23.1 (23.9)	23.0 (24.0)	8.54, 45.1
Proportion (%) of high sensitivity patients	13.9 (20.3)	14.0 (21.2)	8.33, 21.0
ϕ – contribution of feedback	1.59 (25.7)	1.66 (21.2)	0.768, 2.74
Between Subject Variability (CV%)			
η _{ALT.P0}	114 (7.50)	115 (16.4)	97.2, 132
η _{αLS}	119 (10.8)	138 (22.4)	91.5, 147
η _{αHS}	168 (19.4)	170 (39.2)	67.2, 245
η _{kout}	52.2 (6.18)	51.8 (12.7)	44.7, 57.9
Residual Unexplained Variability (CV%)			
σ	39.2 (3.99)	39.0 (23.4)	35.9, 42.4

Conclusions

The relationship between administration of different KF iv dosing regimens and the subsequent elevation in serum ALT was successfully described by the semi-mechanistic PK/PD model developed in cancer patients. The model developed predicts that the dosing schedule selected for phase II studies (650 µg/m² iv 1 h weekly) is associated with an acceptable low risk of severe ALT elevation in advanced cancer patients and provides the scientific basis for KF dose reduction in cancer patients who develop a severe ALT elevation.

[1] Gao J, Hamann MT. Chemistry and biology of kahalalides. Chemical reviews. 2011;111(5):3208-3235.

[2] Fetterly GJ, Owen JS, Stuyckens K, Passarelli JA, Zannikos P, Soto-Matos A, Izquierdo MA, Perez-Ruixo JJ. Semimechanistic pharmacokinetic/pharmacodynamic model for hepatoprotective effect of dexamethasone on transient transaminitis after trabectedin (ET-743) treatment. Cancer chemotherapy and pharmacology. 2008;62(1):135-147.