Baseline tumor volume affects rituximab pharmacokinetics in patients with diffuse large B-cell lymphoma (DLBCL)

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Background

Rituximab is a chimaeric monoclonal antibody targeted against CD20 B-cell antigen. It has profoundly improved the treatment of B-cell malignancies. However, the clinical response is highly variable. Part of this variability is explained by rituximab pharmacokinetic (PK) variability, higher concentrations being associated with a better clinical response. Furthermore, rituximab concentrations were shown to be influenced by tumor burden.

Objectives

- To describe rituximab pharmacokinetics in patients with diffuse large B-cell lymphoma (DLBCL).
- To quantify the impact of initial tumor volume on rituximab pharmacokinetic variability.

Patients and methods

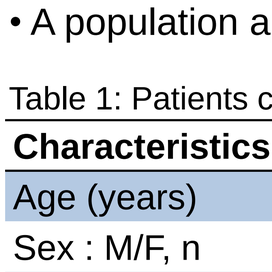
- 108 patients with DLBCL from two prospective multicenter studies were evaluated.
- They received 4 rituximab 375 mg/m^2 infusions every two weeks.
- Rituximab concentrations were measured before and after each rituximab infusion, with additional samples in some patients (day 5 of each cycle, and 2 to 3 weeks after the 4th cycle).
- Baseline metabolic tumor volume (MTV_0) was measured using positron emission tomography (PET).
- A population approach (Monolix® 4.3.2) was applied.

Table 1: Patients characteristics

Characteristics	LNH2007-3B (n=89)	GOELAMS 02.03 (n=19)
Age (years)	47 [19-60]	54 [25-68]
Sex : M/F, n	56/33	7/11
Weight (kg)	74 [47-106]	71 [45-98]
Height (cm)	172 [153-193]	167 [155-180]
BSA (m^2)	1.88 [1.44-2.3]	1.8 [1.4-2.2]
Leucocytes (g/dl)	7.92 [2.81-22.6]	6.2 [3.03-11.4]
Lymphocytes (%)	12.9 [2-44]	1.7 [0.96-2.84]
MTV_0 (cm^3)	461 [16.96-4339]	11.8 [0.8-75.8]

BSA: body surface area; MTV_0: baseline metabolic tumor volume.

Results



Rituximab concentrations were best described using a two-compartment model with first order elimination.
V_1 and V_2 are central and peripheral volumes of distribution, respectively, CL and Q are systemic and distribution clearances, respectively.

- The PK model satisfactorily described rituximab concentrations

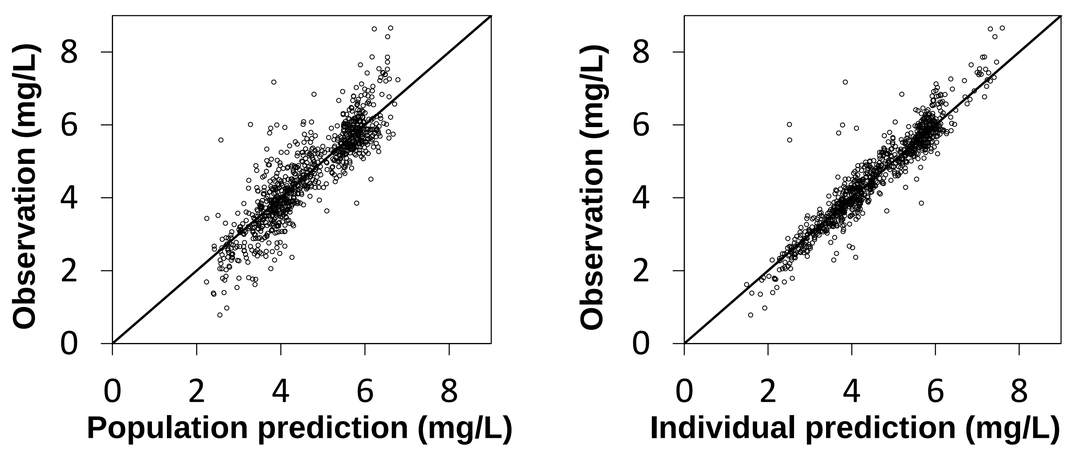


Figure 1: Scatter plots of the final population PK model

Table 2: Final pharmacokinetic parameter estimates

Parameter		Estimate	RSE (%)	*P* (wald)
Clearance, CL (L/h)		0.0232	7	
Central volume of distribution, V_1 (L)		3.96	12	
$\beta_{MTV_0\text{-}V1}$		0.0892	22	8.4×10^{-6}
$\beta_{BSA\text{-}V1}$		1.53	20	3.3×10^{-7}
Distribution clearance, Q (L/h)		0.0863	5	
Peripheral volume of distribution, V_2 (L)		5.32	22	
$\beta_{MTV_0\text{-}V2}$		0.254	14	$<10^{-10}$
$\beta_{BSA\text{-}V2}$		1.57	29	4.9×10^{-4}
Interindividual variability (standard deviation, ω) (%)	CL	48.2	10	
	V_1	28.7	10	
	V_2	27.4	28	
Residual variability (standard deviation, σ)	additive (mg/L)	0.325	9	
	proportional %	4.78	19	

β: covariate influence on a parameter; BSA: body surface area; MTV_0: baseline metabolic tumor volume; RSE: relative standard error.

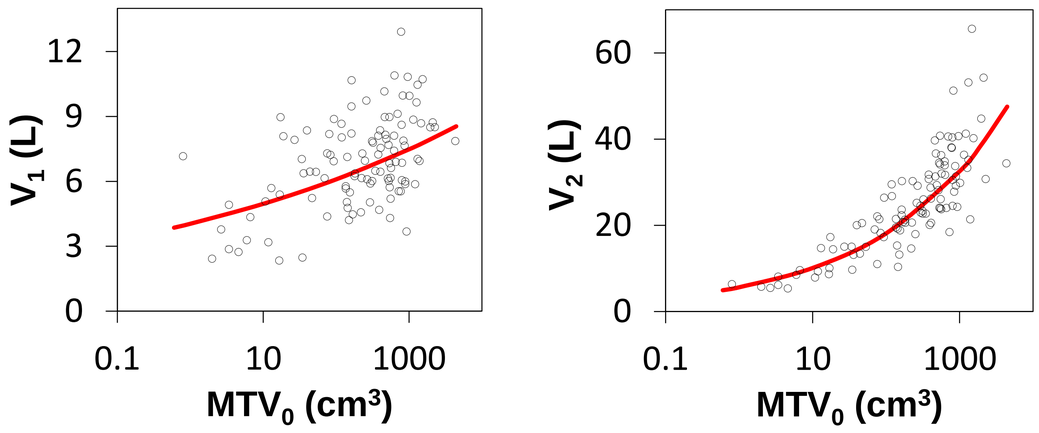


Figure 2: Central (V_1) and peripheral (V_2) volumes of distribution *vs* baseline metabolic tumor volume (MTV_0)

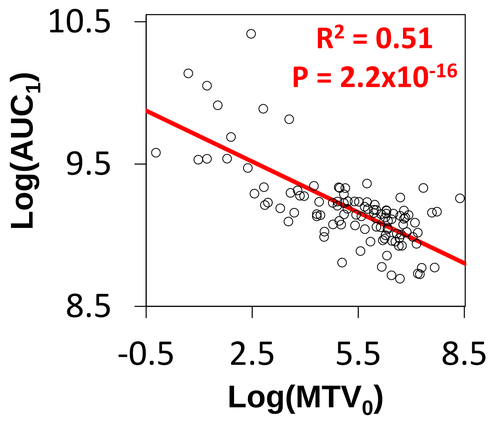


Figure 3: Log of area under concentration-time curve of the cycle 1 (AUC_1) *vs* log of baseline metabolic tumor volume (MTV_0)

	P
AUC_1	***
MTV_0	*

	P
AUC_1	***
MTV_0	

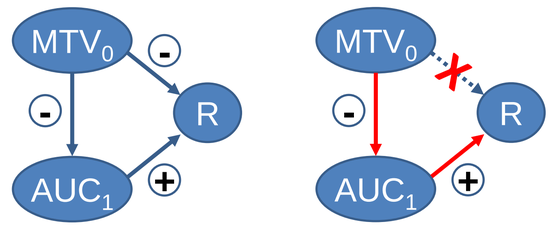


Figure 4: Univariate (left) and multivariate (right) logistic regression analysis. AUC_1: area under concentration-time curve of the cycle 1; MTV_0: baseline tumor volume; R: response; ***: *P*<0.001; *: *P*<0.05.

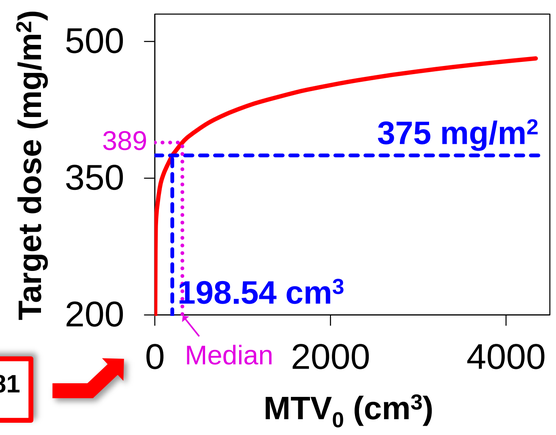
- Final model simulation

$$AUC_1 = \frac{14840}{(MTV_0)^{0.081}}$$

- ROC curve analysis

$AUC_{1,cutoff} = 9667.3\ mg.h/L$

Target dose = 244.3 x $(MTV_0)^{0.081}$



Conclusions

- Increasing initial tumor volume (MTV_0) was associated with a decrease in rituximab exposure in patients with DLBCL
- A better response was observed for higher rituximab exposure
- Usual 375 mg/m^2 dose is suitable for patients with MTV of 198 cm^3