POPULATION PHARMACOKINETIC MODEL OF FLUDARABINE IN PATIENTS UNDERGOING CHIMERIC ANTIGEN RECEPTOR T CELLS THERAPY

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BACKGROUND

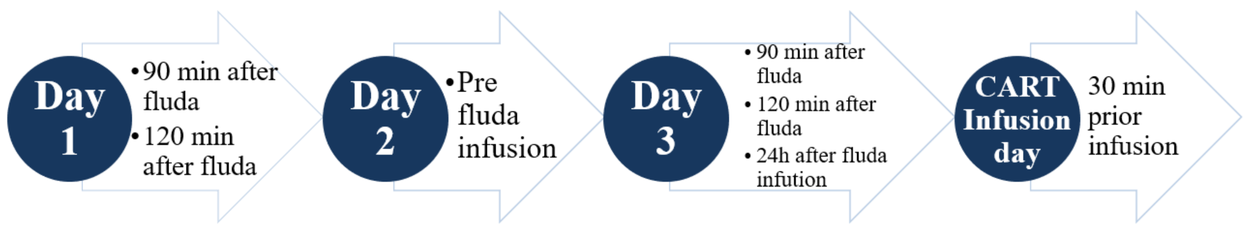
- Optimal fludarabine dosing based on population pharmacokinetic analysis (popPK) can predict outcomes in patients undergoing myeloablative conditioning prior to hematopoietic stem cell transplantation[1,2]
- There is no popPK tailored for patients receiving fludarabine as part of lymphodepleting regimen before chimeric antigen receptor T (CAR-T).

AIM AND OBJECTIVES

- To develop a specific PopPK model of fludarabine in patients undergoing CAR-T cell therapy.

MATERIALS AND METHODS

- Prospective study, patients with r/r LBCL receiving CAR-T therapy with axi-cel or tisa-cel at our institution, between January 2021 and July 2022.
- Fludarabine total dose of 90mg/m² for axi-cel and 75mg/m² for tisa-cel.
- PopPK modelling was performed using nonlinear mixed-effects analysis (NONMEM).



RESULTS

Table 1. Baseline characteristics of the patients included in the population pharmacokinetic model (n=56)

Overall population (n=56)	
Sex; n = male (%)	33 (59)
Age (range)	59 (23 – 82)
Weight (kg)	
Mean (SD)	79.6 (12.9)
Median (range)	82.5 (52 – 101)
Body mass index (kg/m²)	
Mean (SD)	25.2 (3.5)
Median (range)	25.3 (18 – 36.2)
CAR-T construct; n = number (%)	
Axi-cel	38 (68)
Tisa-cel	18 (32)
Histological diagnosis; n (%)	
Diffuse large B-cell lymphoma	30 (54)
Transformed from indolent lymphoma	20 (36)
High-grade B-cell lymphoma	3 (5)
Other*	3 (5)
ECOG	
0	32 (57)
1	20 (36)
2	4 (7)
Prior HSCT	21 (37)
Serum Albumin (g/dL)	
Median (range)	4 (2.7 – 4.8)
Lymphodepletion Therapy	
Outpatient	52 (93)
Inpatient	4 (7)
Renal Function [eGFR: mL/min/1.73 m²]	
Mean (range)	90 (39.04 – 213.91)

- Body size, as represented by actual body weight (ABW) with allometric scaling, was a significant predictor of all pharmacokinetic parameters.
- CAR-T construct and estimated glomerular filtration rate (eGFR) also showed statistical significance for clearance (CL).
- CL was differentiated into a non-renal (4.4 ± 1.2% L/h/70 kg and 3.9 ± 0.95% L/h/70 kg for axi-cel and tisa-cel, respectively) and renal (1.7±1.0%x(eGFR)x(ABW/70)$^{0.75}$ L/h/70 kg) component

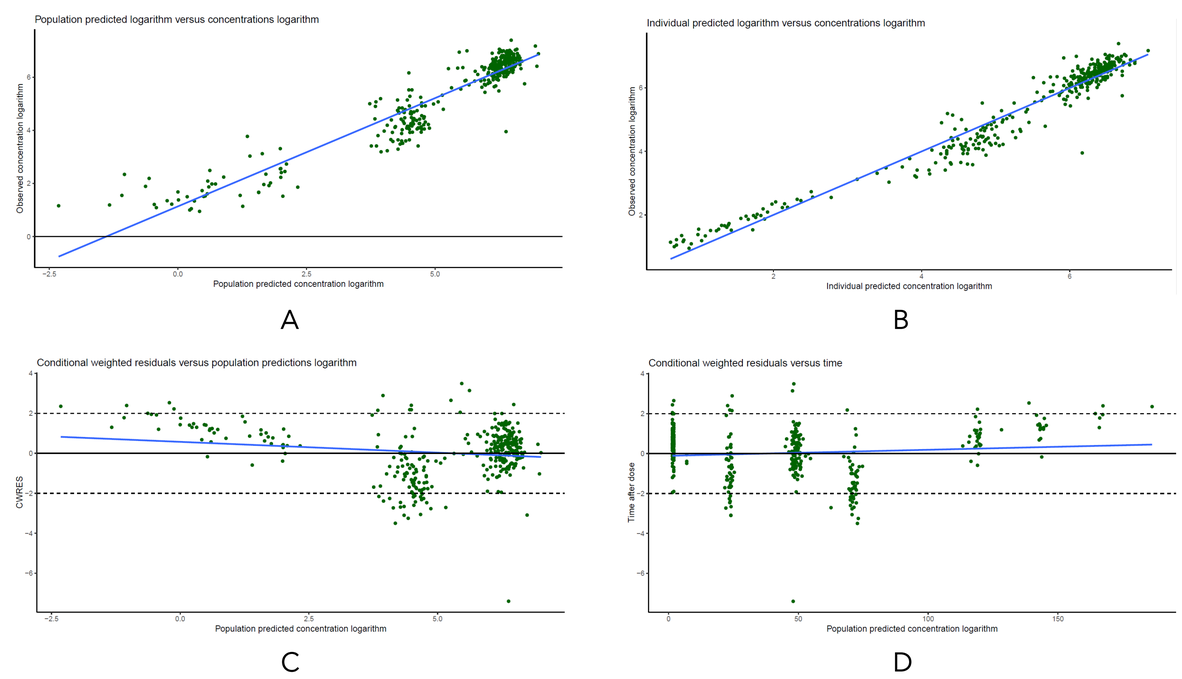


Fig. 1 Goodness-of-fit plots for the final model. **(A)** Observed vs population-predicted logarithm concentrations. **(B)** Observed vs individual-predicted logarithm concentrations. **(C)** Conditional weighted residuals (CWRES) vs population logarithm predictions. **(D)** Conditional weighted residuals (CWRES) vs time (h). Solid black line is the identity line. The blue lines display the trend of the data. Green points represent observed fludarabine serum logarithm

CONCLUSIONS

- Actual body weight , estimated glomerular filtration rate and type of CAR-T are important predictors of fludarabine pharmacokinetics.

REFERENCES

- 1. Langenhorst, Jurgen B et al. "Population Pharmacokinetics of Fludarabine in Children and Adults during Conditioning Prior to Allogeneic Hematopoietic Cell Transplantation." Clinical pharmacokinetics vol. 58,5 (2019): 627-637. doi:10.1007/s40262-018-0715-9
- 2. Langenhorst, J B et al. "Fludarabine exposure in the conditioning prior to allogeneic hematopoietic cell transplantation predicts outcomes." Blood advances vol. 3,14 (2019): 2179-2187. doi:10.1182/bloodadvances.2018029421

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