COMMENTARY

blood advances

TO THE EDITOR:

Chimeric antigen receptor T-cell therapy and fludarabine: precision dosing imperatives

Sebastian G. Wicha,[1] Eva M. A. Wansing,[1-3] Adrin Dadkhah,[2,3] Francis A. Ayuk,[3] Nicolaus M. Kröger,[3] and Claudia Langebrake[2,3]

[1]Department of Clinical Pharmacy, Institute of Pharmacy, University of Hamburg, Hamburg, Germany; [2]University Medical Center Hamburg-Eppendorf, Hospital Pharmacy, Hamburg, Germany; and [3]Department of Stem Cell Transplantation, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

We read with great interest the study by Scordo et al[1] on the identification of an optimal fludarabine exposure target for improved outcomes after axicabtagene ciloleucel therapy for aggressive B-cell non-Hodgkin lymphoma. The study delves into a crucial area of research, attempting to determine the optimal therapeutic intensity of fludarabine in lymphodepletion before CD19 chimeric antigen receptor T-cell therapy. The findings are indeed promising because they suggest that an optimal fludarabine area under the curve (AUC) within the range of 18 to 20 mg·hour/L leads to improved progression-free survival without an increased risk of severe toxicity such as cytokine release syndrome or immune effector–associated neurotoxicity syndrome. Conversely, high AUC levels (>20 mg·h/L) were linked to an increased risk of neurotoxicity and worse outcomes, whereas low AUC levels (18 mg·h/L) correlated with lower progression-free survival.

However, we must emphasize that despite these intriguing findings, several critical issues within the study demand careful consideration. The most prominent concern is the exclusive reliance on estimated AUC based on covariates, without the inclusion of therapeutic drug monitoring (TDM) data for fludarabine. The absence of TDM data has significant implications for the accuracy and clinical relevance of the AUC estimations, given that they are derived solely from patient covariates, including estimated glomerular filtration rate (using the Cockcroft-Gault equation), actual body weight, height, and daily fludarabine dosage using a pharmacometric model.[2]

This overreliance on the pharmacometric model becomes particularly concerning because the model was developed in a different patient population and was not externally validated using cohort-specific pharmacokinetic data. In detail, there are several differences between the model cohort and the population to which it was applied. On the one hand, the model population was significantly younger, with a median age of 18 years compared with 60 years in the present population. On the other hand, the model population consisted of patients receiving fludarabine as part of their conditioning before hematopoietic stem cell transplantation. Thus, the patients received different combination therapies (busulfan, clofarabine, and ATG vs cyclophosphamide) together with fludarabine for different underlying diseases. All in all, applying the model to a clearly different population seems to be problematic in terms of transferability. External validation is crucial to assess the model's generalizability and the reliability of its predictions.[3]

Furthermore, the study's use of creatinine clearance based on the Cockcroft-Gault equation as a surrogate for renal function raises significant precision concerns. The Cockcroft-Gault equation, known to have an uncertainty of around ±20% in up to ~80% of patients, may not accurately reflect true renal function.[4] Given the profound impact of renal function on drug clearance and, consequently, AUC, this choice of covariate may introduce notable imprecision.

Equally concerning is the pharmacometric model's quantification of >30% interpatient variability for clearance. This means that the clearance values estimated for an individual patient with a distinct set of covariates for creatinine clearance, body weight, and height will vary by as much as 30%. This level of

Submitted 30 October 2023; accepted 31 December 2023; prepublished online on *Blood Advances* First Edition 8 January 2024; final version published online 2 February 2024. https://doi.org/10.1182/bloodadvances.2023012068.

uncertainty can only be effectively reduced with the inclusion of individual pharmacokinetic data using TDM. Langenhorst et al themselves evaluated their model in a simulation study that covariate-based dose adjustment would lead to 30% of the patients outside of the target range of 15 to 25 mg·hour/L, whereas TDM-based dosing would leave solely 3% outside of the target.[5] This was well corroborated by Dekker et al[6] in a clinical investigation, who experimentally determined and predicted fludarabine AUC in 26 patients using the model from Langenhorst et al.[2] For 13 patients, the predicted $AUC_{0-\infty}$ was 4 mg·hour/L higher or lower than the true exposure when using only covariates and no TDM data. Moreover, 9 of 11 patients (82%) with a fludarabine $AUC_{0-\infty}$ <14 mg·hour/L were predicted to have a fludarabine $AUC_{0-\infty}$ >14 mg·hour/L, which they determined as a predictor of favorable response.

In summary, the study by Scordo el al reveals a substantial level of variability when estimating AUC without the inclusion of TDM data, raising concerns that the derived very narrow AUC target with only 10% margin may be overly simplified and does not adequately account for individual differences in drug exposure. As a result, the suggested range of 18 to 20 mg·hour/L may not be reliably predictive of optimal dosing.

Contribution: S.G.W. drafted the manuscript; E.M.A.W., A.D., F.A.A., N.M.K., and C.L. provided critical input; and all authors reviewed the manuscript and approved the final version.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

ORCID profiles: N.M.K., 0000-0001-5103-9966; C.L., 0000-0003-1249-4223.

Correspondence: Sebastian G. Wicha, Department of Clinical Pharmacy, Institute of Pharmacy, Universität Hamburg, Bundesstr 45, 20146 Hamburg, Germany; email: sebastian.wicha@uni-hamburg.de.

References

1. Scordo M, Flynn JR, Gonen M, et al. Identifying an optimal fludarabine exposure for improved outcomes after axi-cel therapy for aggressive B-cell non-Hodgkin lymphoma. *Blood Adv*. 2023;7(18):5579-5585.
2. Langenhorst JB, Dorlo TPC, van Maarseveen EM, et al. Population pharmacokinetics of fludarabine in children and adults during conditioning prior to allogeneic hematopoietic cell transplantation. *Clin Pharmacokinet*. 2019;58(5):627-637.
3. Broeker A. Towards precision dosing of vancomycin: a systematic evaluation of pharmacometric models for Bayesian forecasting. *Clin Microbiol Infect*. 2019;25(10):1286.e1-1286.e7.
4. Ainsworth NL, Marshall A, Hatcher H, Whitehead L, Whitfield GA, Earl HM. Evaluation of glomerular filtration rate estimation by Cockcroft–Gault, Jelliffe, Wright and Modification of Diet in Renal Disease (MDRD) formulae in oncology patients. *Ann Oncol*. 2012;23(7):1845-1853.
5. Langenhorst JB, Dorlo TPC, van Kesteren C, et al. Clinical trial simulation to optimize trial design for fludarabine dosing strategies in allogeneic hematopoietic cell transplantation. *CPT Pharmacomet Syst Pharmacol*. 2020;9(5):272-281.
6. Dekker L, Calkoen FG, Jiang Y, et al. Fludarabine exposure predicts outcome after CD19 CAR T-cell therapy in children and young adults with acute leukemia. *Blood Adv*. 2022;6(7):1969-1976.