

TO THE EDITOR:

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

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We read with great interest the study by Scordo et al¹ 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 $\pm 20\%$ in up to $\sim 80\%$ 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

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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 al⁶ 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-∞} 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-∞} <14 mg-hour/L were predicted to have a fludarabine AUC_{0-∞} >14 mg-hour/L, which they determined as a predictor of favorable response.

In summary, the study by Scordo et 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.

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