FLUDARABINE EXPOSURE PREDICTS OUTCOME AFTER CD19 CAR T CELL THERAPY IN CHILDREN AND YOUNG ADULTS WITH ACUTE LEUKEMIA

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INTRODUCTION

The addition of fludarabine to cyclophosphamide as lymphodepleting regimen prior to adoptive transfer of CD19 chimeric antigen receptor (CAR) T cells significantly improves CAR T cell expansion and correlates with a decreased probability of developing a CD19+ relapse (Gardner, 2017). Dosing of fludarabine is currently based on body surface area. We previously showed that this leads to a highly variable plasma exposure that correlates with clinical outcome after allogeneic hematopoietic cell transplantation (Langenhorst, 2019). We therefore hypothesized that optimal exposure of fludarabine might be of clinical importance in the CD19 CAR T setting.

AIM

Examine the effect of fludarabine exposure on clinical outcome following CD19 CAR T cell therapy, including leukemia-free survival, CAR T cell persistence, and the occurrence of CD19-positive relapse, in children and young adults with relapsed/refractory B-ALL

METHOD

- Retrospective analysis with data from 26 patients
- Fludarabine concentrations were measured using a liquid chromatography mass spectrometry method (Punt, 2017)
- The total exposure (Area Under the Curve ($AUC_{0-\infty}$)) was determined using a fludarabine population pharmacokinetic model (Langenhorst, 2019)
- The association of fludarabine with outcome was explored using martingale residuals and further fitted by univariable Cox Proportional Hazards models.
- Kaplan Meier and cumulative incidence curves were plotted and compared with log-rank tests.
- To compare CAR T cell numbers over time in peripheral blood, the AUCs were computed and compared between exposure groups with the Mann-Whitney test.

RESULTS

A retrospective analysis was conducted with data from 26 consecutive patients receiving tisagenlecleucel as treatment for refractory/relapsed B cell acute lymphoblastic leukemia (Table 1). The fludarabine $AUC_{0-\infty}$ was highly variable, resulting in a large range of 8.7-21.8 mg*h/L. Exposure of fludarabine was shown to be a predictor for leukemia-free survival, B cell aplasia, and CD19+ relapse following CAR T cell infusion. Minimal event probability was observed at a cumulative fludarabine exposure ≥14 mg*h/L and underexposure was therefore defined as an $AUC_{0-\infty}$ <14 mg*h/L. In the underexposed group, leukemia free survival was lower (p<0.001; Figure 1A) and the occurrence of CD19+ relapse was higher (p=0.0001; Figure 1B) compared to the group with an $AUC_{0-\infty}$ ≥14 mg*h/L. Furthermore, the duration of B cell aplasia was shorter (p=0.009; Figure 2A) and there was a trend towards a higher AUCs of CAR T cell numbers lower (p=0.07; Figure 2B) in the underexposed group. No significant differences in baseline characteristics were present between the two exposure groups.

Table 1. Patient characteristics. MRD: minimal residual disease; CR: complete remission; allo-HCT: allogeneic hematopoietic cell transplantation.

	All patients
Number of patients	26
Age at infusion, years (range)	14.4 (4.0-24.5)
Male/female	15/11
Follow up, days (range)	389 (53-800)
MRD negative CR on day 28	81%
Indication for CAR T therapy	
Primary refractory	4
Relapse	22
Disease status at start lymphodepletion	
M1 marrow	17
≥ M2 marrow	9
Nr. of prior therapies	
1-2	21
3-5	5
Prior blinatumomab	
Yes	7
No	19
Prior allo-HCT	
Yes	11
No	15

Figure 1. Impact of fludarabine (Flu) on Leukemia-Free Survival (A) and CD19+ relapse (B).

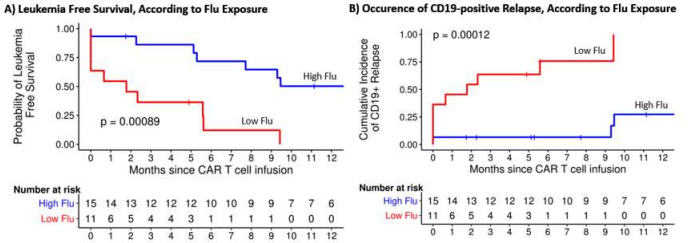
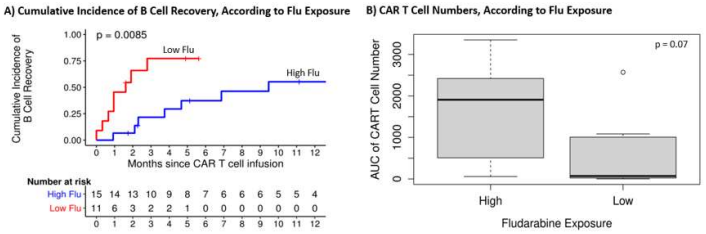


Figure 2. Impact of fludarabine (Flu) on B Cell Recovery (A) and CAR T Cell Expansion (B).



CONCLUSIONS

- A cumulative fludarabine $AUC_{T0-\infty}$ ≥14 mg*h/L correlates with improved leukemia-free survival after CD19 CAR T cell infusion
- Clinical outcome in patients receiving CD19 CAR T cells might be improved by optimizing fludarabine exposure in the lymphodepleting regimen
- Larger studies validating the proposed target, including multivariable analysis and optimal dosing, are needed to improve the efficacy of CD19 CAR T therapy

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