POPULATION PHARMACOKINETICS OF FLUDARABINE (F-ARA-A) IN HEMATOPOIETIC CELL TRANSPLANTATION (HCT) PATIENTS

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INTRODUCTION

Removal of the cell transplant (HCT) is an optimal treatment for patients with advanced hematologic malignancies and bone marrow disorders. Conditioning regimens containing chemotherapy and/or radiation are given prior to allogeneic transplant to eradicate or reduce malignant cell burden, promote engraftment through host immunosuppression and in the case of nonmyeloablative (NMA) regimens allow for graft vs. tumor effect.

Fludarabine phosphate injection (F-ARA-A) is a fluorinated nucleoside analogues with both anti-tumor and immunosuppressive activity and is routinely used in NMA regimens in combination with cyclosporin A, antithymocyte globulin, radiation, and others. The administration it undergoes several enzymatic biotransformations steps to its active metabolites and the excretion of F-ARA-A is through an active transport of F-ARA-A in T-lymphocytes in inhibition of DNA synthesis, ultimately leading to cell death by apoptosis [1].

Although fludarabine is a highly effective agent it has significant dose dependent side effects the most being profound myelosuppression and neurotoxicity [2]. Previous studies identified an association between F-ARA-A exposure measured in plasma and treatment related morbidity and mortality. Patients with F-ARA-A concentrations was higher in patients plasma with area under the curve (AUC0–∞) ≥ 0.65 ng/mL as compared to those patients with an AUC0–∞ > 0.65 ng/mL (50% vs. 15%)(Figure 1) [3].

METHODS

Study Population, Pharmacokinetic Samples, Data

Data for this study were obtained from 87 patients eligible for NMA-BMT and were used for the development of the population pharmacokinetic model and limited sampling strategy. Concentration of fludarabine was measured in plasma from 0 to 24 hour post dose. Fludarabine 40 mg/m²/die i.v. on days 6 – 2 before transplant; total body irradiation 2500 cGy single fraction day 1. Fludarabine phosphatase was administered over 1 hour i.v. on days 6 – 2; Blood samples were collected for F-ARA-A pharmacokinetics with the first dose (day-6) immediately predose and at times 1.6 (100 min), 2.4, 3, 4, 6, 8, 12 and 24 hours post start of infusion. DNA was genotyped for twelve candidate variants in CD73 (CTSE), ENT1 (SLC44A4) and DCR.

Population Pharmacokinetic Modeling and Covariate Selection

Pharmacokinetic spaces were conducted using a non-linear mixed effects model to estimate F-ARA-A clearance (Cl) and volume of distribution (Vd); and computing area under the curve. A step-wise covariate model building strategy of forward inclusion and backward elimination was used to assess the effects of clinical and genetic covariate on F-ARA-A clearance and volume of distribution (Vd). The genetic variants were tested as categorical covariates that could influence F-ARA-A Cl and volume of distribution. Further model evaluation and assessment was performed using non-parametric bootstrap and visual predictive check.

Developed of Limited Sampling Model

The dataset of 87 patients was randomly divided into 2 groups for model development (n=50) and dosing model verification (n=29). The model development group was assessed using a different combinations of limited sampling times that could predict AUC0–∞. Acceptable model equation were identified as using less than 3 sampling time points with an r² >0.9. The model validation group (n=29) was then used to determine the predictive performance of the limited sampling models developed.

MODEL DEVELOPMENT

A total of 784 concentrations from 87 individuals were used for covariate model building and limited sampling strategy development. Patient characteristics are shown in Table 1.

Structural Model:

A 2-compartmental model with intravenous administration (Covariate Figure 1) was performed for an initial estimation of F-ARA-A pharmacokinetics. Figure 3 shows a graphical display of 2-compartment model.

Error Model:

An exponential error model was used to describe subject variability (BIV) and a combined proportional and additive error model was used to describe the residual unexplained variability (BIV).

Covariate Selection:

• The following covarates were assessed: age, gender, CrCl using Cockcroft and Gault equation, height, actual body weight, ideal body weight (IBW), height, weight, body surface area and genotypes.
• CrCl and IBW were found to be significant covariates towards F-ARA-A Cl
• IBW was found to be significant covariate towards V1

Final Model:

F-ARA-A total Cl was modelled as a sum of non-renal and renal contribution. The total Cl was allocatable using UW (Equation 1). The volume of distribution in the central compartment (V1) was predicted to vary based on BW (Equation 2).

To examine goodness of fit, diagnostic plots were assessed during the model development process (Figure 4).

INDIVIDUALIZED DOSE EQUATION FOR PREDICTION OF F-ARA-A AND THE FLUDARABINE DOSE:

Based on the final parameter estimates, a personalized model was developed to predict the CI for the first dose of fludarabine. Fludarabine monophosphate dose can be calculated in 3 steps:

Step 1: Calculate individual’s estimated F-ARA-A clearance (TVCL) based on CrCl and IBW

TVCL = \( \frac{1.76 \times 3.774 \times \text{CrCl}}{(76 + \text{IBW})^{0.75}} \)

Step 2: Calculate the estimated F-ARA-A dose (mg) to achieve the desired AUC target

\( \text{F-ARA - A Dose (mg)} = \frac{\text{Dose (mg)}}{\text{CrCl}} \)

Step 3: Calculate fludarabine monophosphate dose

Fludarabine phosphate = \( \text{F-ARA - A Dose (mg)} \times 1.20 \)

Clinical example of how the model can be applied clinicly is as follows.

Consider a patient with

IBW: 62 kg.

CrCl: 67.5 mL/min

Target AUC = 0.50 μg/mL

Fludarabine phosphate = 43.15 mg x 1.20 = 52 mg

LIMITED SAMPLING STRATEGY:

Model equations were compared using regression concentrations at multiple sampling points against the AICc obtained from the NONMEM model. Models containing 2 or more covariates significantly more accurately predicted AICc vs. as compared to single time points.

The best models were then tested in a validation group containing one-third of the dataset of the model was assessed. The median prediction errors (MPE) and median absolute prediction error (MAPE) were within 3% and thus the models shown in table 3 predicted with lowest bias and highest precision of those tested. Models 2-5 would be acceptable models for clinical use.

CONCLUSION

CrCl and IBW were significant covariates towards F-ARA-A Cl. IBW was an important covariate towards volume of distribution. From these data we developed a fludarabine dosing equation to estimate the dose that can be used to target an optimal AICc in HCT patients. To simply and efficiently monitor fludarabine exposure, we designed a limited sampling strategy for estimation of fludarabine AICc. These tools can now be tested to determine if pharmacokinetic guided dosing can reduce treatment related mortality associated with fludarabine and thereby improve survival in HCT patients. In the future variants within other enzymes modulating conversion of F-ARA-A to F-ARA-ATP should be studied.

REFERENCES