Pharmacokinetic Modeling of Fludarabine to Control Exposure and Improve Outcomes after Reduced Intensity Conditioning Transplantation

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INTRODUCTION AND OBJECTIVES

Treatment related mortality (TRM) remains a problem after allogeneic hematopoietic cell transplant (HCT). Although the use of reduced intensity (RIC) and non-myeloablative conditioning regimens have successfully reduced TRM in elderly and those with comorbidities, TRM still occurs in a substantial number of recipients.(1),(2) Clinical factors such as disease type, comorbidities and stem cell source are important variables towards TRM. However in addition to these factors, the systemic exposure to agents used in the conditioning regimens are important determinants of TRM. Variability in exposure is high; reducing and controlling exposure is important in reducing TRM.

Fludarabine is an immunosuppressive, anticancer agent that is widely used in conditioning regimens. There is extensive data on fludarabine associated side effects, most severe being neurotoxicity. Data suggest that some adverse effects are dose or exposure dependent. Fludarabine is rapidly and almost completely dephosphorylated to its metabolite, F-ara-A. Fludarabine is partially renally cleared and those with low creatinine clearance (CrCl) accumulate F-ara-A. Currently fludarabine is dosed on a fixed mg/m2 basis, and dose reductions for low CrCl, if reduced at all, is empiric and imprecise. In our previous studies we demonstrated that in patients undergoing RIC HCT with a plasma F-ara-A area under the curve ($AUC_{0-\infty}$) ≥6.5 μg*hr/mL they had a significantly higher risk of TRM than those with $AUC_{0-\infty}$ < 6.5 μg*hr/mL (50% vs 15%, p<0.01).(2) To reduce the risk of high and variable exposure to F-ara-A, we recently developed a dosing equation that personalizes the dose of fludarabine to achieve any desired plasma exposure.(3) This model uses CrCl and ideal body weight to predict an individual's F-ara-A clearance (CL) from which an optimal dose is estimated. However, prior to using the model to dose patients an assessment of model directed dosing is necessary. In this study we sought to evaluate the use of the equation by testing its ability to predict clinical outcomes. The objective of this study was to retrospectively test the performance of the equation by assessing the relationships between equation predicted $AUC_{0-\infty}$, and TRM, acute graft vs host (GVHD) disease and engraftment.

METHODS

Patients: Two hundred and forty patients who underwent allogeneic RIC HCT and received cyclophosphamide, fludarabine, TBI with or without anti-thymocyte globulin were selected for the analysis (Table 1). Fludarabine dose, actual body weight, height and serum creatinine on day of admission, post transplant immunosuppressive therapy, demographic data, day of TRM, acute GVHD and engraftment were obtained from transplant database on each subject.

Estimation of F-ara-A $AUC_{0-\infty}$ in each subject: Each individuals estimated F-ara-A CL (L/hr) was calculated using equation 2 in box below with ideal body weight (IBW) derived from the Devine equation and pretransplant CrCl using Cockcroft and Gault. Once F-ara-A clearance was estimated then the AUC that the patient was likely exposed was calculated using equation 3.

F-ara-A equivalent dose (mg) = Administered fludarabine dose (mg) / 1.28……..…Eq.1

F-ara-A CL (L/hr) = [7.04 + 3.9 x {(CrCl/85) x (70/IBW)}] x $(IBW/70)^{0.75}$ ……..Eq.2

F-ara-A $AUC_{0-\infty}$ (ug*hr/mL) = administered dose in F-ara-A equivalents (mg)/ F-ara-A CL (L/hr)……..Eq. 3

Clinical outcomes: TRM was defined as death due to any cause other than relapse or disease progression. GVHD was staged and graded according to the standard GVHD criteria based on clinical and pathological criteria. Day of neutrophil engraftment was the first of 3 consecutive days of an absolute neutrophil count > 500 cell/uL by day 42.

Statistical analysis: Recursive partitioning regression analysis was used to select optimal cut points for F-ara-A CL and F-ara-A $AUC_{(0-\infty)}$ towards each of the clinical outcomes. Once optimal cut points were identified the cumulative incidence of engraftment, TRM and aGVHD (grade II-IV) above and below each of the cutpoints was calculated using death prior to event as a competing risk.

Cox proportional hazards regression was used to evaluate the effect of F-ara-A CL and F-ara-A $AUC_{(0-\infty)}$ towards TRM at day 100 and month 6, aGVHD at 6 month, and engraftment at day 42 adjusting for donor source, HLA group, disease risk and comorbidity score.

Table 1: Patient characteristics

No. of Subjects	240
Fludarabine dose (mg) , median (range)	67 (42-100)
Age (years), median (range)	58.6 (18.8-75.1)
Male	57.9%
Transplant Source Marrow PBSC cord blood	 43.33% 47.5% 9.16%
Unrelated/sibling donor	47.5/52.5%
Primary Disease ALL AML CML Myelodysplasia Lymphoma Multiple Myeloma Other	 9.2% 29.6% 2.5% 16.7% 21.3% 7.5% 13.4%

RESULTS

Relationships between $AUC_{0-\infty}$ and Clinical Outcomes:

Treatment Related Mortality

- The overall TRM was 8% and 13% at day 100 and 6 months, respectively. The median (range) time to TRM was 165 days (18-1518) .
- Cumulative incidence of TRM was significantly higher at day 100 in those with lower F-ara-A clearance (Fig 1) and higher F-ara-A $AUC_{0-\infty}$ (Fig 2 and Table 2).

Acute Graft vs Host Disease

- Grade II-IV aGVHD rate was 43% at 6 months. Lower F-ara-A CL was associated with higher risk of aGVHD after adjusting for donor source (Fig 3 and Table 3).
- F-ara-a $AUC_{0-\infty}$ was not associated with aGVHD after adjusting for donor source.

Engraftment:

- Neutrophil engraftment was achieved in 96% of patient. In an univariate analysis, none of the pharmacokinetic parameters were associated with engraftment.

Table 2: Multiple regression analysis of TRM at day 100 and 6 months

Factor	Hazard Ratio (95% CI) at 100 days	p	Hazard Ratio (95% CI) at 6 mos	p
F-ara-A $AUC_{(0-\infty)}$				
<6 μg*hr/mL	1.00		1.00	
≥6μg*hr/mL	5.30 (1.59-17.71)	0.01	2.42 (0.87-6.77)	0.09
Stem Cell Source				
Related	1.00		1.00	
Unrelated (UR)	4.32 (1.16-16.06)	0.03	2.79 (1.06-7.31)	0.04
UR cord blood	1.91(0.55-6.67)	0.31	1.71 (0.70-4.13)	0.24
Comorbidity score				
0	1		1	
1-2	2.27 (0.72-7.13)	0.16	2.42 (1.04-5.62)	0.04
≥3	2.83 (0.83-9.57)	0.10	1.72 (0.66-4.48)	0.27
Acute GVHD				
no	1.00		1.00	
yes	1.89 (0.71-5.00)	0.20	2.35 (1.07-5.15)	0.03

Table 3: Multiple regression analysis of aGVHD II-IV at 6 months

Factor	TRM Hazard Ratio (95% CI) at 100 Days	P
F-ara-A CL		
<13 L/hr	1.00	
≥13 L/hr	0.44 (0.19-1.02)	0.05
Stem Cell Source		
Related	1.00	
Unrelated (UR)	1.76 (1.08-2.87)	0.02
UR Cord Blood	0.75 (0.69-1.66)	0.75

Figure 1: TRM at day 100 above and below F-ara-A CL 8.5 L/hr

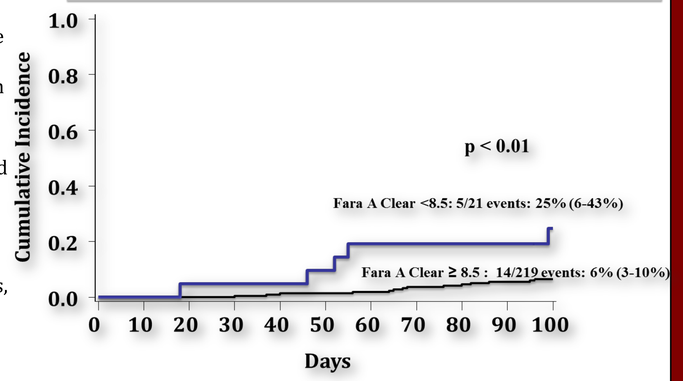


Figure 2: TRM at day 100 above and below F-ara-A AUC 6μg*hr-mL

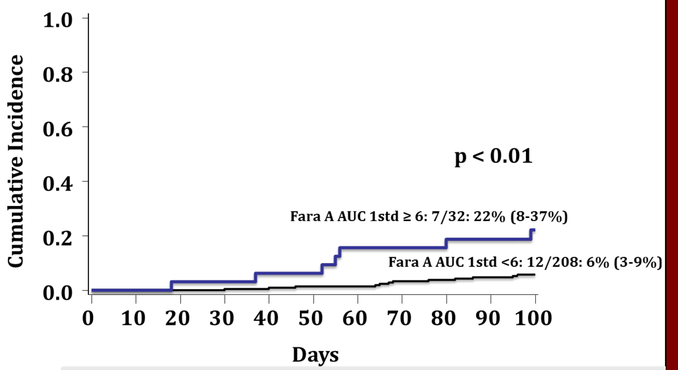
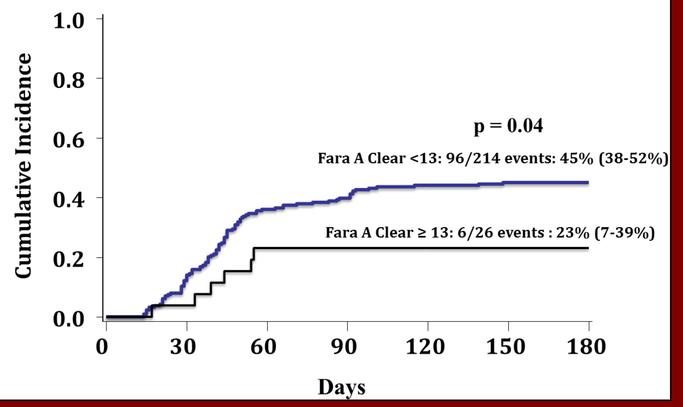


Figure 3: aGVHD grades II-IV at day 180 above and below F-ara-A CL 13 L/hr



CONCLUSIONS AND FUTURE DIRECTIONS

We recently developed a dosing equation to personalize the fludarabine dose in RIC regimens. To evaluate the value of personalized dosing we conducted a retrospective analysis to associate equation predicted F-ara-A clearance and F-ara-A $AUC_{0-\infty}$ to clinical outcomes. We found that low F-ara-A clearance and a high F-ara-A $AUC_{0-\infty}$ are significantly associated with TRM and aGVHD. F-ara-A clearance and $AUC_{0-\infty}$ was not associated with engraftment. These data support selecting the fludarabine dose using our equation which accounts for CrCl and ideal body weight. Future studies should be directed at further defining the optimal plasma exposure and the minimal amount of F-ara-A needed for sufficient efficacy.

(1) Kharfan AM et al. Cancer Control. 2012 Jan;19(1):68-75; (2) Long-Boyle JR, et al. Bone Marrow Transplant. 2011 Jan;46(1):20-6; (3) Sanghavi K. et al. Clin Pharmacol Ther, Vol 85, S87, March 2014 (Abstract)