Biol Blood Marrow Transplant 23 (2017) 1701–1713

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Pharmacokinetics and Model-Based Dosing to Optimize Fludarabine Therapy in Pediatric Hematopoietic Cell Transplant Recipients

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Article history:
Received 19 April 2017
Accepted 25 June 2017

Key Words:
Pharmacokinetics
Pharmacodynamics
Fludarabine
Pediatric
Allogeneic
Hematopoietic cell transplantation

A B S T R A C T

A prospective multicenter study was conducted to characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of fludarabine plasma (f-ara-a) and intracellular triphosphate (f-ara-ATP) in children undergoing hematopoietic cell transplantation (HCT) and receiving fludarabine with conditioning. Plasma and peripheral blood mononuclear cells (PBMCs) were collected over the course of therapy for quantitation of f-ara-a and f-ara-ATP. Nonlinear mixed-effects modeling was used to develop the PK model, including identification of covariates impacting drug disposition. Data from a total of 133 children (median age, 5 years; range, .2 to 17.9) undergoing HCT for a variety of malignant and nonmalignant disorders were available for PK-PD modeling. The implementation of allometric scaling of PK parameters alone was insufficient to describe drug clearance, particularly in very young children. Renal impairment was predicted to increase drug exposure across all ages. The rate of f-ara-a entry into PBMCs (expressed in pmoles per million cells) decreased over the course of therapy, resulting in 78% lower f-ara-ATP after the fourth dose (1.7 pmoles/million cells [range, .2 to 7.2]) compared with first dose (7.9 pmoles/million cells [range, .7 to 18.2]). The overall incidence of treatment-related mortality (TRM) was low at 3% and 8% at days 60 and 360, respectively, and no association with f-ara-a exposure and TRM was found. In the setting of malignancy, disease-free survival was highest at 1 year after HCT in subjects achieving a systemic f-ara-a cumulative area under the curve (cAUC) greater than 15 mg*hour/L compared to patients with a cAUC less than 15 mg*hour/L (82.6% versus 52.8% $P = .04$). These results suggest that individualized model-based dosing of fludarabine in infants and young children may reduce morbidity and mortality through improved rates of disease-free survival and limiting drug-related toxicity. ClinicalTrials.gov Identifier: NCT01316549

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INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) is used to treat a variety of pediatric disorders. Although they differ in the level of myelosuppression, many current preparative regimens are fludarabine based. Fludarabine is a nucleoside analogue used for its antileukemia activity and to enhance stem cell engraftment through its potent immunosuppressive activity against B and T lymphocytes [1,2]. Administered intravenously as a prodrug, fludarabine monophosphate (f-ara-AMP) undergoes rapid dephosphorylation in the plasma to the systemically circulating compound, f-ara-a. F-ara-a is then transported from the plasma into cells by several uptake transporters, including equilibrative nucleoside transporters (ENT1, ENT2) and the concentrative nucleoside transporter 3 [3-6]. In the cytoplasm, f-ara-a is sequentially phosphorylated to the active triphosphate species (f-ara-ATP), which inhibits DNA synthesis and RNA production, inducing apoptosis [1,2,7].

Financial disclosure: See Acknowledgments on page 1712.
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http://dx.doi.org/10.1016/j.bbmt.2017.06.021
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However, despite the widespread use of fludarabine, there is a lack of pharmacokinetic (PK) studies in children undergoing HCT to optimize dosing and clinical outcomes. Outside the setting of HCT, only 2 published studies reported PK data for fludarabine in children. These were phase I/II studies evaluating fludarabine administered by continuous infusion in combination with cytarabine for the treatment of relapsed leukemias and solid tumors in children [8,9]. Limited in sample size, these studies did not include very young children (<1 year of age) and were unable to sufficiently evaluate how patient-specific clinical factors may contribute to fludarabine PK variability. Furthermore, quantification of the active intracellular species, f-ara-ATP, was only performed in 4 subjects with excess white blood cells.

In adult HCT recipients, the PK of f-ara-a is variable and population PK (PopPK) analyses have identified several clinical covariates contributing significantly to drug clearance (CL), including weight and renal function, which are important clinical factors relative to children and drug exposure [10-14]. Two of the largest studies to date reported a strong association between f-ara-a exposure and risk of treatment-related adverse outcomes in adult HCT, demonstrating the need for improved dosing strategies to optimize drug therapy [11,15]. Several studies in adults with cancer or undergoing HCT for malignant disease have also attempted to define the relationship between fludarabine dose, plasma concentrations, and intracellular f-ara-ATP drug levels, with both in vitro and in vivo investigations observing large variability in intracellular concentrations of f-ara-ATP [16-23].

Understanding the relationships between f-ara-a and f-ara-ATP is critical to improving dosing strategies in children. This study's primary objective was to evaluate patient-specific factors responsible for variability in fludarabine exposure. Secondly, we aimed to identify relationships between fludarabine exposure and clinical outcomes.

PATIENTS AND METHODS

Study Population

This was a prospective PK study of fludarabine in children who underwent HCT for a variety of malignant and nonmalignant pediatric disorders. Patients were eligible to participate in PK-pharmacodynamic (PD) analysis if they were between 0 and 17.99 years old, met protocol-specific eligibility criteria for transplantation, and were to undergo an allogeneic or autologous HCT with gene therapy that included intravenous fludarabine monophosphate as part of the conditioning regimen. Patients who received fludarabine monophosphate alone or in combination with other agents given over 3 to 5 days were eligible to participate. Fludarabine PK data were collected between 2010 and 2015 at the University of California San Francisco Benioff Children's Hospital, the University of Minnesota Masonic Children's Hospital, and Boston Children's Hospital. All local institutional review boards approved this study and written informed consent/assent was obtained from all patients. The study was registered at ClinicalTrials.gov as NCT01316549.

PK Sampling

Blood collection times were selected by an optimal sampling strategy for population analysis utilizing prior f-ara-a PK data available in adults and D-optimality methods [11,24,25]. Collection times for f-ara-ATP were incorporated into the optimal sampling time based on literature estimates for time to maximum concentration and half-life [18,26]. Blood collections were performed on 2 different occasions over the course of fludarabine therapy for a total of 10 blood samples. Fludarabine was administered intravenously over 30 to 60 minutes in all patients. On the first occasion, blood samples for the quantification of f-ara-a were collected at 2, 4, 8, and 24 hours after the start of fludarabine infusion. Sampling was then repeated after a subsequent dose of fludarabine at 2 and 24 hours after the start of infusion. On both occasions, blood collection for f-ara-ATP analysis occurred at concurrent sampling times as f-ara-a (2 and 24 hours after infusion) in patients enrolled at the University of California San Francisco clinical site only (n = 66).

Plasma and intracellular drug concentrations were processed independently. For the quantification of f-ara-a in the plasma, 1 mL of whole blood was collected at each time point in a K_2 EDTA tube and placed on wet ice. All plasma samples were centrifuged at 3500 rpm for 10 minutes at 4°C within 30 minutes of collection, and the plasma was removed and stored at -70°C until analysis. Blood samples to be assayed for f-ara-ATP were collected in a 4-mL cell preparation tube with sodium citrate and processed for recovery of peripheral blood mononuclear cells (PBMCs) as previously described [27]. For each sample, cells were stained with trypan blue and isolated PBMCs were counted using the manual hemocytometer method. Results for f-ara-ATP were normalized and presented as pmoles per million cells.

Bioanalysis of F-Ara-a and F-Ara-ATP

Plasma and PBMC samples were analyzed for f-ara-a and f-ara-ATP using 2 different validated liquid chromatography-tandem mass spectrometry methods, as previously described [28,29]. The fara-a assay was linear in the range of 2 ng/mL to 800 ng/mL. The mean accuracies (mean ± coefficient of variation) of the f-ara-a assay were 98.5% ± 7.0, 101.7% ± 6.6, and 92.8% ± 7.8 at low-, medium-, and high-quality control levels, respectively.

To measure f-ara-ATP in PBMCs, cells (~5 million) were collected and lysed with 1-mL 70% methanol containing 1.2 mM tris buffer. The lysate was mixed with an internal standard and injected into an API5000 liquid chromatography-tandem mass spectrometry system (AB SCIEX Pte. Ltd. Ontario, Canada). The linear range of the intracellular assay was 1.52 to 76 nM. The mean accuracies (mean ± coefficient of variation) were 100.7% ± 9.5, 94.0% ± 10.5, 96.3% ± 9.5 at the low-, median-, and high-quality control levels, respectively.

PopPK Analysis

A nonlinear mixed effects modeling approach using NONMEM 7.3 software (Icon Development Solutions, Hanover, MD) [30] was used to describe the time course of f-ara-a and f-ara-ATP concentrations. R software version 3.2.0 was used for graphical inspection of the results [31]. An equivalent dose of f-ara-a (molecular weight 285 g/mol) to that of the administered monophosphate form (f-ara-AMP, molecular weight 365 g/mol) was calculated and used for model building. Both f-ara-a and f-ara-ATP concentrations that fell below the lower limit of quantification were reported by the lab and entered into the model as the true value. The first-order conditional estimation method with interaction was used to estimate PK parameters and variability. Model selection was based on objective function values and goodness-of-fit plots. Residual unexplained variability was characterized separately for plasma and intracellular compartments by a proportional error model.

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