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Pretransplant Absolute Lymphocyte Counts Impact the Pharmacokinetics of Alemtuzumab

Rebecca A. Marsh [1,2,*], Tsuyoshi Fukuda [2,3], Chie Emoto [2,3], Lisa Neumeier [1,2], Pooja Khandelwal [1,2], Sharat Chandra [1,2], Ashley Teusink-Cross [1,2], Alexander A. Vinks [2,3], Parinda A. Mehta [1,2]

[1] *Division of Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children's Hospital, Cincinnati, Ohio*
[2] *Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio*
[3] *Division of Pharmacology, Cincinnati Children's Hospital, Cincinnati, Ohio*

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A B S T R A C T

Alemtuzumab is frequently used as part of reduced-intensity conditioning (RIC) regimens for allogeneic hematopoietic cell transplantation (HCT) in pediatric patients with nonmalignant diseases. We previously suggested an optimal day 0 targeted range of alemtuzumab, but there are no pediatric data regarding the pharmacokinetics (PK) of subcutaneous alemtuzumab to guide precision dosing trials. The goal of this study was to prospectively characterize alemtuzumab PK and to explore absolute lymphocyte count (ALC) as a predictor of interindividual variability. We prospectively enrolled 23 patients who received an alemtuzumab, fludarabine, and melphalan RIC regimen. Seventeen patients completed study and received 1 mg/kg alemtuzumab divided over 5 days subcutaneously, starting on day −14. The median age was 7 years (range, .5 to 18). Blood sampling for PK measurements and descriptive PK analyses were performed. The median maximum alemtuzumab concentration was 2.39 μg/mL (interquartile range, 1.98 to 2.92). The median terminal half-life was 5.2 days (interquartile range, 2.7 to 7.8). The median concentration at day 0 was 1.27 μg/mL (interquartile range, .35 to 1.51). Importantly, day 0 alemtuzumab levels and area under the curve negatively correlated with predose ALC and ALC area-time, respectively. In conclusion, we reported the PK of subcutaneous alemtuzumab given to pediatric allogeneic HCT patients and observed that almost all patients have persistence of lytic levels of alemtuzumab beyond day 0, at levels in excess of that needed to reduce the risk of acute graft-versus-host disease. Additionally, levels correlate with pretransplant ALC. These results will allow the development of population PK models for precision dosing trials.

INTRODUCTION

Alemtuzumab is frequently used as part of reduced-toxicity and reduced-intensity conditioning (RIC) regimens for the allogeneic hematopoietic cell transplantation (HCT) of pediatric and young adult patients with nonmalignant diseases [1-7]. Regimens typically include alemtuzumab with fludarabine and melphalan or with fludarabine and busulfan. The former is often used for the transplantation of patients with primary immune deficiencies, inborn errors of metabolism, and bone marrow failure syndromes [1-6]. The latter has predominantly been used for patients with chronic granulomatous disease, although its use is expanding [7,8].

Alemtuzumab is a humanized monoclonal antibody against CD52 that is expressed by most lymphocytes. The pharmacokinetics (PK) of alemtuzumab are inherently complicated. There is significant interpatient variability with regard to clearance of alemtuzumab, because the initial clearance depends on the availability of CD52 antigen [9,10]. With early administration the availability of CD52 results in rapid consumption of alemtuzumab due to target-mediated clearance that, in turn, results in an initial higher elimination clearance and shorter half-life. After depletion of CD52, alemtuzumab clearance decreases, resulting in an increase in the half-life. The package insert (Campath [alemtuzumab], Genzyme Corporation, Cambridge, MA) reports that alemtuzumab half-life ranges from 2 to 32 hours after a first dose in patients with B cell chronic lymphocyte leukemia, but the terminal half-life ranges from 1 to 14 days after repeated dosing. The terminal half-life in adult bone marrow transplant patients who received alemtuzumab intravenously has been reported to range from 2 to 3 weeks [9].

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* Correspondence and reprint requests: Rebecca A. Marsh, MD, Division of Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children's Hospital, 3333 Burnet Avenue, Cincinnati, OH 45229.
E-mail address: Rebecca.marsh@cchmc.org (R.A. Marsh).

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Currently, no pediatric data are available regarding the PK of alemtuzumab to support its dosing in pediatric regimens and no PK data after subcutaneous administration in pediatric patients. Pediatric and young adult subcutaneous dosing in current clinical use is not uniform and in fact is highly variable. Variations in practice and preference for subcutaneous or intravenous administration is typically center dependent. Our center began using subcutaneous alemtuzumab approximately 10 years ago because of the association with decreased infusion reactions, which has been recently documented by another group [11]. Commonly used transplant regimens may include alemtuzumab doses of .5, .6, 1, or 1.5 mg/kg, or dose-escalation schedules also exist that administer escalating doses of 3, 10, 15, and 20 mg (or 3, 10, 10, and 10 mg in smaller patients weighing < 10 kg), resulting in extremely wide ranges of doses if expressed per kg body weight [1-8,12]. Additional variability is found with regard to days of administration in relation to the graft infusion, with the last dose of alemtuzumab being given in either the third week before, second week before, or the week of transplant. This results in highly variable alemtuzumab exposure to the donor graft, which in turn affects the extent of lymphocyte/T cell depletion of the graft. Previous studies have demonstrated a relationship between the dose and timing of alemtuzumab administration and the risk of acute graft-versus-host disease (GVHD) [6,12,13]. In addition, alemtuzumab dosing affects the risk of developing mixed chimerism and early immune reconstitution after alemtuzumab, fludarabine, and melphalan RIC HCT regimens [6,12,14,15]. Most importantly, we recently demonstrated that the risk of acute GVHD depends on the peritransplant (day 0) plasma concentration of alemtuzumab [16]. Nonlytic levels (<.1 to 0.15 μg/mL) [16] are associated with a high risk of acute GVHD, whereas lytic levels protect against acute GVHD. On the contrary, very high peritransplant levels of alemtuzumab were associated with a high risk of developing mixed chimerism and also adversely affected early post-transplant immune recovery.

Taken together, these data suggest that a targeted optimal alemtuzumab exposure is needed for each patient undergoing allogeneic HCT with an alemtuzumab-containing regimen to improve their overall outcome. Dosing can be individualized to ensure a lytic level on day 0, which will decrease the risk of acute GVHD, but target the level such that it is not too high to convey an unreasonable increased risk of mixed chimerism or adversely affect immune reconstitution. Our goal was to first characterize alemtuzumab PK in pediatric patients undergoing allogeneic HCT and to explore absolute lymphocyte count (ALC) as an influential determinant for the interindividual variability. Here we report results of our prospective study of the PK of subcutaneous alemtuzumab given to pediatric patients undergoing allogeneic HCT using an alemtuzumab, fludarabine, and melphalan containing RIC regimen.

METHODS

Patients, Transplant Regimen, and Alemtuzumab Dosing

Institutional review board approval was obtained for this study. Twenty-three patients with nonmalignant diseases receiving an alemtuzumab, fludarabine, and melphalan containing RIC HCT regimen were prospectively enrolled. Three patients elected to withdraw from study to avoid the frequent blood sampling. Seventeen patients received a uniform 1 mg/kg alemtuzumab divided over 5 days subcutaneously, starting on day –14, and were included in the final data analysis. (The remaining 3 patients were treated with other schedules of alemtuzumab.) Patient demographics and transplant information are described in Table 1. The median age was 7 years (range, .5 to 18), and diagnoses were predominantly primary immune deficiencies, except for 1 patient with idiopathic aplastic anemia. Fludarabine was given as 30 mg/m^2 per dose on days –8 to –4 (1 mg/kg in patients weighing < 10 kg). Melphalan was given as 140 mg/m^2 per dose on day –3 (4.7 mg/kg in patients weighing < 10 kg). Patients received methylprednisolone and either cyclosporine or tacrolimus for acute GVHD prophylaxis. All patients received antimicrobial prophylaxis, intravenous immune globulin replacement, and supplemental nutritional support per standard clinical practice. ALCs were recorded from the daily complete blood count results obtained as part of routine clinical care.

A total of 1 mg/kg alemtuzumab was given subcutaneously over 5 days starting on day –14. The total dose was either divided equally over 5 days or, if the total dose was greater than 15 mg (in patients weighing > 15 kg), the first day's dose was limited to 3 mg and the remainder of the 1-mg/kg total dose was divided over the remaining 4 days. Patients were given premedications including acetaminophen, diphenhydramine, and corticosteroids before each dose of alemtuzumab as per standard clinical care. No anaphylaxis or other serious reactions such as hypotension, difficulty breathing, or hives were observed in any of the patients.

Alemtuzumab Measurement

Blood samples were drawn for PK measurement at predose, 30 minutes, and 8 hours after each dose, followed by daily levels until day +2 and weekly levels for 8 weeks. Additional samples were drawn 15 minutes before and 8 hours after graft infusion. Whole blood samples drawn from patients were processed to obtain plasma, which was frozen until measurement. We modi-

Table 1
Patient Demographics and Transplant Information

Patient	Age (yr)	Diagnosis	Conditioning Regimen Chemotherapy	GVHD Prophylaxis	Patient and Donor HLA Match	Donor Relation	Graft Source
1	11	Aplastic anemia	Flu/Mel	CSA, MP	10/10	Unrelated	Marrow
2	18	CGD	Flu/Mel	CSA, MP	10/10	Unrelated	PBSC
3	6	HLH	Flu/Mel	CSA, MP	10/10	Sibling	Marrow
4	7	HLH	Flu/Mel	CSA, MP	9/10	Unrelated	Marrow
5	2	IPEX	Flu/Mel	Tacro, MP	9/10	Unrelated	Marrow
6	5	HLH	Flu/Mel	CSA, MP	10/10	Unrelated	Marrow
7	2	HLH	Flu/Mel	CSA, MP	10/10	Unrelated	Marrow
8	15	CID	Flu/Mel	CSA, MP	10/10	Unrelated	PBSC
9	11	HLH	Flu/Mel	Tacro, MP	9/10	Unrelated	Marrow
10	1	HLH	Flu/Mel	CSA, MP	10/10	Sibling	Marrow
11	14	HLH	Flu/Mel	CSA, MP	10/10	Sibling	Marrow
12	15	HLH	Flu/Mel	CSA, MP	10/10	Unrelated	Marrow
13	10	CGD	Flu/Mel	CSA, MP	9/10	Unrelated	Marrow
14	4	HLH	Flu/Mel	CSA, MP	10/10	Sibling	Marrow
15	.5	SCID	Flu/Mel	CSA, MP	10/10	Unrelated	Marrow
16	3	IPEX	Flu/Mel	Tacro, MP	10/10	Unrelated	Marrow
17	11	HLH	Flu/Mel	CSA, MP	10/10	Unrelated	Marrow

Flu/Mel indicates fludarabine and melphalan; CSA, cyclosporine; MP, methylprednisolone; PBSC, peripheral blood stem cell; IPEX, immune deficiency, polyendocrinopathy, X-linked; Tacro, tacrolimus; CID, combined immune deficiency.