Clinical Research: Pediatric

A Prospective Study of Alemtuzumab as a Second-Line Agent for Steroid-Refractory Acute Graft-versus-Host Disease in Pediatric and Young Adult Allogeneic Hematopoietic Stem Cell Transplantation

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Pooja Khandelwal [1,2,*], Chie Emoto [3], Tsuyoshi Fukuda [2,3], Alexander A. Vinks [2,3], Lisa Neumeier [1], Christopher E. Dandoy [1,2], Javier El-Bietar [1,2], Sharat Chandra [1,2], Stella M. Davies [1,2], Jacob J. Bleesing [1,2], Michael B. Jordan [1,2,4], Parinda A. Mehta [1,2], Sonata Jodele [1,2], Michael S. Grimley [1,2], Ashish Kumar [1,2,5], Kasiani C. Myers [1,2], Rebecca A. Marsh [1,2]

[1] Division of Bone Marrow Transplantation and Immune Deficiency, Cancer and Blood Diseases Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
[2] Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio
[3] Division of Clinical Pharmacology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
[4] Division of Immunobiology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
[5] Division of Experimental Hematology, Cincinnati Children's Hospital, Cincinnati, Ohio

A B S T R A C T

We describe a single-center prospective study of alemtuzumab as a second-line agent for steroid-refractory (SR) acute graft-versus-host disease (aGVHD) in pediatric and young adult allogeneic hematopoietic stem cell transplant recipients. Alemtuzumab was administered for grades II to IV aGVHD if patients did not improve within 5 days or worsened within 48 hours after corticosteroids. Interim analyses of alemtuzumab levels and response were performed after every 5 patients enrolled, resulting in 3 dosing cohorts, as follows: (1) .2 mg/kg alemtuzumab subcutaneously on days 1 to 5 (maximum of 31 mg over 5 days) and .2 mg/kg/dose (not exceeding 10 mg/dose) on days 15, 22, and 29; (2) .2 mg/kg alemtuzumab subcutaneously on days 1 to 5 (maximum of 43 mg over 5 days) and .2 mg/kg/dose on day 7, 10, 15, 22, and 29; and (3) .2 mg/kg subcutaneously on days 1 to 5 and .2 mg/kg/dose on day 7, 10, 15, and 22. Alemtuzumab levels were assessed before starting alemtuzumab and at days 1, 3, 6, 10, and 14 and weekly until day 99, where day 1 was the day of first alemtuzumab dose. Fifteen patients (median age, 10 years; range, 1.4 to 27) received alemtuzumab for grades II (6%), III (74%), and IV (20%) SR-aGVHD. The overall response rate was 67%, with complete response (CR) in 40%, partial response (PR) in 27%, and no response in 33%. The median day 6 alemtuzumab level was 2.79 μg/mL (interquartile range, 1.34 to 4.89) in patients with CR compared with .62 μg/mL (interquartile range, .25 to 1.45) in patients with PR + no response ($P < .05$). Ninety percent (n = 9) of patients with a CR or PR reduced corticosteroid doses within 8 weeks from first alemtuzumab dose. Side effects included fever (26%) and transient thrombocytopenia (53%). Asymptomatic viremias occurred in all patients but invasive viral disease occurred in 2 patients. One patient developed Epstein-Barr virus–post-transplantation lymphoproliferative disorder. Eighty percent (n = 12) of patients were alive at 6 months, of whom 53% (n = 8) were free of GVHD whereas 13% (n = 2) developed chronic GVHD. Alemtuzumab is an effective second-line agent for children and young adults with SR-aGVHD. Higher alemtuzumab levels are associated with CR. A real-time dose adjusted alemtuzumab study is needed to further optimize the dose of alemtuzumab in aGVHD.

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INTRODUCTION

Steroid-refractory (SR) acute graft-versus-host disease (aGVHD) is a significant complication of allogeneic hematopoietic stem cell transplantation (HCT) and is a leading cause of morbidity and nonrelapse mortality [1,2]. No clear second-line agent for the treatment of SR-aGVHD exists currently,

largely because most second-line agents [3-6] have similar somewhat disappointing outcomes. Alemtuzumab is a humanized IgG1 monoclonal antibody that targets cells expressing the CD52 antigen, including T, natural killer, and B lymphocytes, and a proportion of monocytes and dendritic cells [7]. Alemtuzumab is licensed for use in fludarabine-refractory B cell chronic lymphocytic leukemia [8], but it has also found a role in T cell tumors in adults [9] and in autoimmune diseases [10]. Alemtuzumab is commonly used as part of reduced-intensity conditioning regimens for allogeneic HCT [11] and can decrease the incidence of aGVHD [12,13]. Several adult case reports and case series have reported successful use of alemtuzumab for the treatment of SR-aGVHD [14-21] and SR-chronic GVHD [22]. We have previously reported our experience with alemtuzumab as a salvage therapy in SR-aGVHD, which resulted in an overall response rate of 73% [23], but there are no prospective studies of alemtuzumab use as a second-line agent in pediatric patients. Here we describe the results of a single-center prospective clinical trial evaluating alemtuzumab as a second-line agent for SR-aGVHD in pediatric and young adult allogeneic HCT recipients.

METHODS

The Cincinnati Children's Hospital Medical Center's institutional review board granted permission for this study. Patients with SR-aGVHD were enrolled between 2012 and 2014, if they were between 3 months and 40 years of age, had grade II or higher aGVHD, and had only received steroids for treatment. Ongoing uncontrolled life-threatening infections, prior anaphylaxis to alemtuzumab, and waning whole blood donor chimerism were criteria for exclusion from study.

The treating physician made a clinical diagnosis of aGVHD based on consensus criteria [24], supported by biopsies when clinically indicated. *SR-aGVHD* was defined as progression of aGVHD after 48 hours of ≥2 mg/kg steroids or lack of response after 5 days of ≥2 mg/kg steroids. Institutional practice at the time of study allowed for the increase of steroids from 2 mg/kg/day to 4 mg/kg/day if response was unsatisfactory initially.

No additional immune suppression apart from corticosteroids was allowed on study and patients were taken off study if additional immune suppression was initiated.

Treatment with Alemtuzumab

Optimal alemtuzumab dosing for treatment of aGVHD in pediatric patients has not been established. We performed an interim analysis of response to alemtuzumab after every 5 enrolled patients completed treatment to adjust the treatment schedule and limit the number of children receiving suboptimal therapy, based on alemtuzumab levels, clinical responses, and complications.

The first 5 patients received alemtuzumab according to the following defined schedule, based on the results of our retrospective study results [23]. Patients received 1 mg/kg alemtuzumab subcutaneously, divided over 5 days with a maximum total dose of 31 mg for the first 5 days. The physician had the option of using a test dose of 3 mg alemtuzumab if the initial dose of .2 mg/kg exceeded this dose. In this case, the difference between the planned total 1 mg/kg 5-day dose and the test dose was divided over the remaining 4 days. After the first 5 days of alemtuzumab, patients received .2 mg/kg alemtuzumab subcutaneously (not exceeding 10 mg/dose) on days 15, 22, and 29, where day 1 was the first day of alemtuzumab administration.

After interim analysis of the first 5 patients, the total dose of alemtuzumab in the first 5 days was increased from a maximum of 31 mg to 43 mg, and additional alemtuzumab doses were added on days 7 and 10. This was done to ensure maintenance of a level well above the lytic threshold during the first 2 weeks, as 2 patients had levels of .1 µg/mL to .2 µg/mL on days 6 to 10, which is at the lytic threshold. Both patients had no response at day 7 and were taken off study to receive additional aGVHD treatment, so we judged this level to be inadequate. After enrollment of 5 additional patients, we eliminated the day 29 dose to lower the duration of alemtuzumab exposure, as 1 patient in this group was observed to maintain detectable levels of alemtuzumab for 2 months after the last dose.

Assessment of Response

We recorded aGVHD stage and grade information at the time of alemtuzumab administration, at weekly intervals for 15 weeks after the first alemtuzumab course, and 6 months after the first alemtuzumab course. Responses were evaluated either at 4 weeks after first alemtuzumab dose, if patients were on study, or until they were taken off study and additional immune suppression was added, whichever occurred first. A *complete response* (CR) to alemtuzumab was defined as resolution of GVHD, documented by a reduction in the grade of GVHD to 0 by 4 weeks after the first dose of alemtuzumab. A *partial response* (PR) was defined as improvement in GVHD by at least 1 stage in at least 1 organ at weeks from the first dose of alemtuzumab without worsening of stage of GVHD in other organs. *No response* (NR) was defined as progression of aGVHD symptoms or lack of response, leading to escalation of immune suppression with additional therapeutic agents. *Relapse of GVHD* was defined as new aGVHD in any organ in patients who had a prior CR to alemtuzumab within 6 months of receiving the first dose of alemtuzumab. Relapses were not assessed for patients who were off study.

Alemtuzumab Levels

Venous blood for assessment of alemtuzumab levels was collected at the following time points: at enrollment (onset of aGVHD), before first alemtuzumab dose (day1), days 3, 6, 10, and 14, and then weekly until 14 weeks after first alemtuzumab dose or until escalation of immune suppression with additional agents, which ever came first. Plasma samples were frozen until analysis. Alemtuzumab levels were measured using a flow cytometry method modified from the methodology of Rebello and Hale [25]. Detailed methodologies are available on request.

Adverse Effects

Patients were monitored for evidence of known complications of alemtuzumab, including hypersensitivity, rash, fever, thrombocytopenia, and neutropenia. Results of clinical microbiologic testing were followed until 6 months from first alemtuzumab dose for evidence of infectious complications, including blood, broncho-alveolar lavage, tissue cultures, and PCRs when applicable, and the results of serial peripheral blood cytomegalovirus, Epstein-Barr virus (EBV), and adenovirus PCRs, which were performed weekly or twice weekly per routine clinical practice.

Antimicrobial Prophylaxis, Viral Infections, and Treatment before Alemtuzumab

All patients received antimicrobial prophylaxis as per institutional practice against fungi and *Pneumocystis jerovicii*. All patients were receiving viral prophylaxis at the time of alemtuzumab. All patients received intravenous immunoglobulin replacement.

Survival

Survival data including day and cause of death was collected until 6 months from the first dose of alemtuzumab.

Statistical Analysis

Statistical differences in alemtuzumab levels were assessed with non-parametric comparisons for each pair using the Wilcoxon method using JMP software (version 12, SAS Institute Inc., Cary, NC).

RESULTS

Fifteen patients with a median age of 10 years (range, 1.4 to 27 years) received alemtuzumab for treatment of SR-aGVHD after allogeneic HCT. Patient demographics are shown in Table 1. The children were diagnosed with aGVHD grades 2 to 4 at a median of 49 days (range, 25 to 142 days) after HCT. aGVHD was diagnosed in 1 patient after administration of donor lymphocytes to treated mixed chimerism. All patients were initially treated with steroids, were receiving a median dose of 4 mg/kg (range, 2 mg/kg to 4 mg/kg) at the time of alemtuzumab administration, and had been receiving steroids for a median of 5 days (range, 2 to 14 days) after aGVHD diagnosis. No patient was started on topical steroids for acute skin GVHD after initiating alemtuzumab therapy but topical steroid therapy initiated before starting alemtuzumab was continued during alemtuzumab administration. One patient with acute skin and liver GVHD received alemtuzumab on day 14 of corticosteroid therapy because this patient developed acute liver GVHD 8 days after initiation of treatment of steroids for acute skin GVHD and demonstrated worsening over the next 5 days. The majority of children were treated for grade 3 GVHD (n = 11, 74%), whereas 1 had grade 2 GVHD and 3 had grade 4 GVHD (Table 2).