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Alemtuzumab for the Treatment of Steroid-Refractory Acute Graft-Versus-Host Disease

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ABSTRACT

The treatment of steroid-refractory acute graft-versus-host disease (aGVHD) remains a clinical challenge, for which no standard therapy exists. Alemtuzumab is a humanized anti-CD52 monoclonal antibody (mAb) that has been successfully used as part of conditioning regimens for hematopoietic stem cell transplantation (HSCT) to prevent GVHD. The purpose of this study was to evaluate the safety and efficacy of alemtuzumab in treating steroid-refractory aGVHD (≥grade II) following HSCT. Eighteen patients received subcutaneous alemtuzumab 10 mg daily on 5 consecutive days. Response was assessed at day 28 following initiation of alemtuzumab. Eight patients had grade II aGVHD, 8 had grade III, and 2 had grade IV. The main organ involved was the liver in 4 patients, gastrointestinal (GI) tract in 5, skin in 3, skin and liver in 3, and skin and GI tract in 3. Fifteen patients (83%) responded to alemtuzumab, including 6 (33%) with complete response. All 3 unresponsive patients died of GVHD. Ten of 15 responders are alive at median follow-up of 11 months (range: 3-24). Infections occurred in 14 patients, including cytomegalovirus (CMV) reactivation in 11. Grade 3 neutropenia and thrombocytopenia occurred in 6 and 4 patients, respectively. Alemtuzumab was well tolerated, and induces promising response rates in steroid-refractory aGVHD.

KEY WORDS

Acute GVHD • Alemtuzumab • Campath-1H • Monoclonal antibody • Stem cell transplantation • Steroid refractory

INTRODUCTION

Graft-versus-host disease (GVHD) remains an important cause of mortality of allogeneic hematopoietic stem cell transplantation (HSCT). The incidence of acute GVHD (aGVHD) may vary from 20% to 70%, depending on several factors [1-2]. Corticosteroids are the current standard initial treatment for aGVHD, with approximately 50% of patients achieving an initial response [3-5]. However, no consensus exists on the optimal treatment of patients who are unresponsive or refractory to steroid therapy. To date, a number of therapeutic agents have been evaluated for the treatment of steroid-refractory GVHD, including high-dose corticosteroids, antithymocyte globulin (ATG), mycophenolate mofetil (MMF), tacrolimus, sirolimus, pentostatin, etanercept, and a variety of monoclonal antibodies (mAbs) [6-14].

Alemtuzumab (Campath-1H) is an unconjugated, humanized IgG1 kappa mAb that targets the CD52 antigen expressed on T and B lymphocytes, monocytes, monocyte-derived dendritic cells, macrophages, and eosinophils [15-20]. The Campath-1 family of antibodies was initially developed in the early 1980s as T cell-depleting (TCD) agents to prevent GVHD in the allogeneic HSCT setting [18,21]. Alemtuzumab is currently indicated for the treatment of patients with fludarabine-refractory B cell chronic lymphocytic

leukemia (CLL) [15,22]. Data from recent studies suggest the potential role of alemtuzumab in minimizing GVHD when used as part of the conditioning regimen for allogeneic HSCT [23-27]. In addition, alemtuzumab has been used successfully to treat established steroid-refractory, severe aGVHD, although only anecdotal data are available [28-30]. Based on these data, we conducted a prospective clinical study to evaluate the safety and efficacy of alemtuzumab in the treatment of steroid-refractory aGVHD in a cohort of 18 allografted patients.

PATIENTS AND METHODS

Eligibility Criteria

Patients were eligible if they had received allo-HSCT from either family donors or unrelated cord blood cells, and had a diagnosis of ≥ grade II aGVHD refractory to corticosteroid therapy, as defined by the Consensus criteria [31]. Patients with uncontrolled infections, cardiac failure, or serum creatinine ≥2 mg/dL or who were receiving immunosuppressive agents other than calcineurin inhibitors and corticosteroids were excluded from this trial. Patients in corticosteroid therapy who initially responded but recurred with their first taper were not eligible. All patients provided written informed consent, and the study protocol was approved by the local Ethics Committee.

Diagnosis of Steroid-Refractory GVHD and Evaluation of Response

The initial evaluation and grading of aGVHD was primarily based on clinical findings. Diagnosis was supported by skin, liver, or gastrointestinal (GI) tract biopsy results whenever indicated and clinically possible. Patients had received initial treatment for GVHD with corticosteroids given at a dose equivalent to 2 mg/kg of MP. Steroid-refractory GVHD was defined as nonresponse to corticosteroids administered for at least 5 consecutive days or progression after 48 hours of therapy. Twice a week GVHD organ stage scores, overall clinical grade, and relevant differential diagnosis were recorded. Responses were assessed for each involved organ. Complete response (CR) was defined as the complete resolution of GVHD at day 28. Partial response (PR) was defined as improvement in at least 1 organ by at least 1 full stage in the absence of progression in any other organ, allowing for a decrease in the dose or discontinuation of corticosteroids. No response (NR) was defined as no reduction in any GVHD organ staging within 14 days or progression of GVHD. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 3.0.

Alemtuzumab Treatment and Anti-Infective Prophylaxis

Alemtuzumab was administered subcutaneously at a dose of 10 mg daily for 5 consecutive days. One infant patient who weighed 10 kg received a lower dose, a total of 15 mg divided across 5 consecutive days. All patients received alemtuzumab as second-line therapy. The administration of cyclosporine (CsA) continued during alemtuzumab treatment, and in patients achieving a response, corticosteroids were slowly tapered, by a 25% reduction in dose every week.

All patients received anti-infective prophylaxis at the start of GVHD treatment, including trimethoprim-sulfamethoxazole for *Pneumocystis jirovecii* pneumonia, fluconazole, or itraconazole for fungal infections, and acyclovir for herpes virus reactivation. Cytomegalovirus (CMV) infection was monitored weekly by CMV pp65 antigenemia testing; if the test result became positive, patients were treated preemptively with valganciclovir.

Statistical Analysis

Patients responsive and unresponsive to alemtuzumab treatment were compared on the basis of their clinical characteristics. Categoric variables were compared using Fisher's exact test, and continuous values were compared using the Student's *t*-test. Survival analysis was estimated according to the Kaplan-Meier method.

RESULTS

Patient Characteristics

All HSCT procedures were performed at the Hospital Universitario in Monterrey and Centro de Hematología y Medicina Interna de Puebla. Eighteen patients were eligible for this trial between November 2004 and February 2007, all of whom were evaluable for efficacy and safety. Baseline patient characteristics are summarized in Table 1. The main organ involved was the liver in 4 patients, GI tract in 5, skin in 3, skin and liver in 3, and skin and GI tract in 3.The median age of the patients was 37 years (range: 1-59), and 10 patients (56%) had grade III or IV aGVHD. No prior therapy other than corticosteroids and CsA was used. The median time to onset of aGVHD was 45 days (range: 14-180), with 8 patients developing late-onset aGVHD (after day 100) as defined by the recent NIH Working Group report [32]. Myeloablative conditioning regimen was used in 1 patient and a fludarabine-based reduced-intensity conditioning regimen was used in 17 patients [33-35]. Seventeen patients had received peripheral blood stem cells (PBSCs) obtained from HLA-identical siblings, and 17 patients received GVHD prophylaxis with CsA 3-5 mg/kg in combination with a short course of methotrexate (MTX) on days 1, 3, and 5 or 6 following HSCT. One patient received unrelated cord blood cells, 5/6

Table 1. *Baseline Clinical Characteristics*

Characteristics	No. of patients (%)
Age, years	
Median	37
Range	1-59
Sex	
Female	11 (61)
Male	7 (39)
Diagnosis	
Acute myelogenous leukemia (AML)	5 (28)
Acute lymphocytic leukemia (ALL)	2 (11)
Chronic myelogenous leukemia (CML)	5 (28)
Multiple myeloma (MM)	2 (11)
Chronic lymphocytic leukemia (CLL)	1 (5.5)
Non-Hodgkin lymphoma (NHL)	1 (5.5)
Myelodysplastic syndrome (MDS)	1 (5.5)
Langerhans' cell histiocytosis (LCH)	1 (5.5)
Donor	
HLA-identical sibling	17 (94)
Unrelated cord blood	1 (6)
Conditioning regimen	
Reduced intensity (RIC)	17 (94)
Myeloablative	1 (6)
Source of stem cell	
Peripheral blood	17 (94)
Cord blood	1 (6)
GVHD prophylaxis	
CsA + methotrexate	17 (94)
CsA + prednisone	1 (6)
GVHD grade	
II	8 (44)
III	8 (44)
IV	2 (11)
Main organ involved	
Liver	4
GI tract	5
Skin	3
Skin and liver	3
Skin and GI tract	3

CsA indicates cyclosporine; GVHD, graft-versus-host disease; GI, gastrointestinal.

HLA compatible, and this patient received GVHD prophylaxis with CsA without MTX. No donor lymphocyte infusion (DLI) was used in any patient.

Response

Fifteen of the 18 patients (83%) responded to alemtuzumab. Six patients (33%) achieved CR, and 9 patients (50%) achieved PR. Five of the 6 patients with CR maintained CR without additional therapy with a median duration of 8 months, and 1 developed disease flare after steroid withdrawal after being in CR for 2 months; this patient was treated with a second course of alemtuzumab and PR was observed. Among 4 of the 6 patients who achieved CR, the main organ involved was the GI tract. Responses by grade of GVHD at study entry and stage of organ involvement are listed in Table 2. Patients with CR or PR were able to decrease the steroid dose by 60% at 28 days of treatment. Two of the 9 patients who achieved PR received additional therapy with anti-CD20 antibody and thalidomide. At the time of last follow-up, 8 of the 15 responders were receiving a median steroid dose of 20 mg on alternate days. Alemtuzumab treatment failed in 3 patients; in 2 of these cases, the primary organs involved were the bowel and skin, and in the remaining patient, the primary organ affected was the liver. In this group of nonresponding patients, steroid therapy was continued at the standard 2 mg/kg/day dose. Results from the univariate analyses of clinical characteristics between responders and nonresponders showed no differences in the main organ involved, GVHD grade, and time between HSCT and GVHD onset.

Survival

Ten of the 18 patients are still alive at a median follow-up of 11 months (range: 3-24) after alemtuzumab treatment. Survival curves after treatment with alemtuzumab are shown in Figure 1. Actual median survival for the patients with PR and NR are 8 and 2 months, respectively. The 3 patients not responding to alemtuzumab died of GVHD at 25, 40, and 90 days after initiation of therapy. The 5 other deaths were attributed to disease relapse, bronchiolitis obliterans, and infectious complications. Among the 6 patients achieving CR, 1 patient relapsed of underlying disease 9 months after alemtuzumab therapy and is receiving salvage therapy. Extensive chronic GVHD (cGVGD) has occurred in 4 of the 10 surviving patients, and 1 other patient has developed limited cGVHD. Five patients showed no signs of cGVHD.

Safety

After a median follow-up of 9 months (range: 2-23) 14 patients (78%) had 1 or more infectious episodes; 2 patients developed septicemia followed by multiorgan system failure and died 60 and 90 days after initiation of alemtuzumab treatment. One patient had fatal pneumonia of bacterial origin, which developed 6 months after alemtuzumab therapy, and 2 additional patients developed bacterial pneumonia requiring hospital admission but responded to antibiotic treatment. These 3 patients previously received valganciclovir because of asymptomatic CMV reactivation, all resolved before pneumonia developed. Pulmonary tuberculosis was identified early in 1 patient and was successfully treated with broad-spectrum antibiotics. Asymptomatic CMV reactivation occurred in 11 patients documented by positive antigenemia requiring preemptive ambulatory valganciclovir therapy. No invasive fungal infections were observed.

Adverse events such as chills, low-grade fever, and headache were observed in 5 patients. Grade 3 neutropenia occurred in 6 patients, and grade 3 thrombocytopenia in 4 patients. No lymphoproliferative disorders have been observed in this group of patients.

Table 2. *GVHD Stage, Response, and Current Status*

Patient Age/Sex	Diagnosis	GVHD Stage (Skin-Liver-Gut)	Alemtuzumab Start (Day Post-SCT)	GVHD Grade	Response, Day 28	Current Status (Day Post-Alemtuzumab*)
27/F	AML	1-0-1	23	II	PR	D, sepsis (60)
25/M	ALL	2-0-1	49	II	PR	D, sepsis (90)
27/F	CML	1-0-1	26	II	NR	D, GVHD (25)
53/F	CML	3-0-0	115	II	PR	cGVHD (698)
55/F	CML	3-0-0	110	II	PR	cGVHD(515)
33/M	NHL	2-0-4	42	III	NR	D, GVHD (40)
57/M	CML	2–2-1	128	III	PR	D, relapse (547)
18/M	AML	2-3-0	43	III	PR	D, infection (210)
15/M	AML	1-1-0	158	II	PR	D, cGVHD (450)
59/F	MM	0-1-4	105	IV	CR	No GVHD (560)
53/M	MDS	2-4-0	183	IV	NR	D,GVHD (90)
1/F	LCH	2-1-3	19	III	CR	No GVHD (420)
53/F	AML	3-0-0	185	II	CR	cGVHD (300)
16/F	ALL	2-3-0	108	III	CR	No GVHD (180)
57/F	CLL	0-0-3	40	III	CR	No GVHD (180)
21/F	AML	3-1-0	45	III	PR	cGVHD (65)
43/F	MM	1-0-4	22	III	CR	No,GVHD (90)
38/F	CML	3-1-0	43	II	PR	cGVHD (65)

AML indicates acute myelogenous leukemia; ALL, acute lymphocytic leukemia; CML, chronic myelogenous leukemia; MM, multiple myeloma; MDS, myelodysplastic syndrome; LCH, Langerhans' cell histiocytosis; PR, partial response; CR, complete response; NR, no response; D, dead; GVHD, graft-versus-host disease; cGVHD, chronic GVHD.

*Day after alemtuzumab.

Lymphocyte counts dropped during the first week after alemtuzumab treatment and remained low (<500 cells/μL) for the subsequent 2 to 8 weeks (mean duration of 6 weeks).

DISCUSSION

The treatment of steroid-refractory GVHD remains a therapeutic challenge. Results from recent studies for salvage therapy after steroid failure are summarized in Table 3 [9,11-13,36-42]. Treatment with alemtuzumab therapy induces an overall response rate of 83% and a CR rate of 33%, which is favorable or comparable to other agents currently under investigation. Bordigoni et al. [36] recently found a response rate of 90% after daclizumab administration, which was higher than 83% demonstrated in our trial; of note, few patient suffered from severe grades III-IV

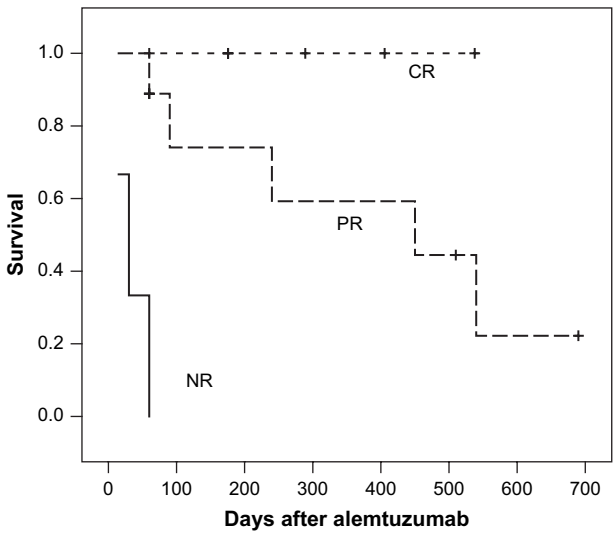

Figure 1. Kaplan-Meier plot of overall survival based on response to alemtuzumab therapy.

Table 3. *Summary of Studies for Steroid-Refractory GVHD*

Agent	N	Overall Response or Improvement	Study
Antithymocyte globulin	79	54%	MacMillan et al., 2002 [11]
	47	57%	MacMillan et al., 2007 [41]
ABX-CBL (anti-CD147)	48	56%	MacMillan et al., 2007 [41]
Mycophenolate mofetil	10	60%	Krejci et al., 2005 [40]
Pentostatin	23	74%	Bolanos-Meade et al., 2005 [9]
Etanercept	13	46%	Busca et al., 2007 [37]
Denileukin diftitox	30	71%	Ho et al, 2004 [39]
Basiliximab (anti–IL-2 receptor)	23	83%	Schmidt-Hieber et al., 2005 [42]
Dacluzimab (anti-CD25)	43	51%	Przepiorka et al, 2000 [13]
	62	90%	Bordigoni et al., 2006 [36]
Infliximab (anti–TNF-α)	32	59%	Patriarca et al, 2004 [12]
Visilizumab (anti-CD3)	44	32%	Carpenter et al., 2005 [38]

TNF-α indicates tumor necrosis factor-α; GVHD, graft-versus-host disease.

aGVHD at the beginning of daclizumab therapy, and 56% of them had steroid-dependent aGVHD.

In our study, notably, treatment with alemtuzumab resulted in the tapering of steroid therapy in the majority of responding patients, by at least 60% of the initial steroid dose after 28 days from treatment initiation. Furthermore, our study is 1 of the first to examine salvage therapy of late-onset (>100 days) aGVHD. In the present study, 8 patients developed acute manifestations of GVHD beyond day 100 from HSCT, 6 of whom achieved PR. Recently the NHI Consensus Conference recognized a late aGVHD (after day 100); we included this group of patients with a clinical picture of aGVHD who should be treated with a shorter treatment interval of more intensive immunosupression to control acute inflammatory manifestations. Although results from the univariate analysis suggest that none of the clinical characteristics examined were predictive of response to alemtuzumab therapy, the number of patients in this study was small. Hence, these results will require further investigation in a larger clinical trial. In our centers the use of matched unrelated HSCT is done using only cord blood cells, and occasionally we use mismatched HSCT; therefore, only 1 patient who received unrelated cord blood cells was included.

As expected, infections were a common complication of alemtuzumab therapy, emphasizing the need to adhere to anti-infective prophylaxis and close monitoring for infections. With a median follow-up of 9 months (range: 2-23), 3 patients developed infectious complications and died, all of whom had PR and remained dependent on corticosteroid therapy. CMV reactivation was common, and most incidences developed shortly after lymphocyte nadir, which occurred between weeks 2 and 4 after initiation of alemtuzumab. All patients with CMV reactivation were successfully treated with valganciclovir; importantly, no progression to CMV disease was observed.

Treatment with alemtuzumab was well tolerated, with only 5 patients developing headache, low-grade fever, and/or chills after the first dose. None of the patients developed injection-site skin reactions. Transient cytopenia occurred in 6 patients; thrombocytopenia was most common after 2 weeks, and neutropenia after 3 weeks of alemtuzumab therapy. No patient required blood component transfusions or growth factor support. In the majority of patients, cytopenias resolved within 6 weeks of onset. Lymphopenia, which is attributable to the direct consequence of the pharmacologic action of alemtuzumab, was the most common hematologic toxicity. Epstein-Barr virus (EBV)-related lymphoproliferative disorders were not observed in this study. Although therapeutic agents that may affect T cell function after allogeneic HSCT raise concerns for engraftment and control of disease, none of the patients in our study developed graft rejection; in the 2 patients with relapse of underlying disease, 1 had ongoing GVHD and the other maintains complete chimerism without signs of GVHD.

The results of this study suggest that subcutaneous alemtuzumab can be safely administered in patients with steroid-refractory aGVHD, and that it is associated with a promising response rate. Further studies are warranted to confirm our findings in a larger patient population and also in the setting of unrelated HSCT, in order to determine the optimal dose and duration of treatment and to explore the possibility of a maintenance schedule.

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