Published in final edited form as:

Pediatr Transplant. 2014 February ; 18(1): 94–102. doi:10.1111/petr.12183.

The successful use of alemtuzumab for treatment of steroid-refractory acute graft-versus-host disease in pediatric patients

Pooja Khandelwal¹, Julia Lawrence², Alexandra H. Filipovich¹, Stella M. Davies¹, Jacob J. Bleesing¹, Michael B. Jordan^{1,3}, Parinda Mehta¹, Sonata Jodele¹, Michael S. Grimley¹, Ashish Kumar^{1,4}, Kasiani Myers¹, and Rebecca A. Marsh¹

¹Division of Bone Marrow Transplantation and Immune Deficiency, Cancer and Blood Diseases Institute, Cincinnati Children's Hospital, Cincinnati, OH, USA

²Division of Pharmacy, Cincinnati Children's Hospital, Cincinnati, OH, USA

³Division of Immunobiology, Cincinnati Children's Hospital, Cincinnati, OH, USA

⁴Division of Experimental Hematology, Cincinnati Children's Hospital, Cincinnati, OH, USA

Abstract

SR-aGVHD remains a significant cause of morbidity and mortality in allogeneic HCT recipients. Alemtuzumab has been used with success in adult patients but has not been studied in the pediatric setting. To estimate the effectiveness of alemtuzumab for the treatment of SR-aGVHD in pediatric patients, we retrospectively reviewed the charts of 19 patients (median age 4 yr, range 0.5–28 years) with grades II (n = 3), III (n = 10), or IV (n = 6) SR-aGVHD who received alemtuzumab treatment. Patients received a median dose of 0.9 mg/kg alemtuzumab (range 0.3–2 mg/kg) divided over 2–6 days. Eighty-nine percent of patients received additional courses. A complete response, defined as GVHD of grade 0 at four wk following the first alemtuzumab course, was observed in nine patients (47%). A partial response, defined as an improvement in grade after four wk, was observed in five patients (26%). There was no response in five patients (26%). The overall response rate at four wk was 73%. Infectious complications included bacteremia (47%), presumed or documented fungal infections (21%), adenovirus viremia (52%), EBV viremia (36%), and CMV viremia (36%). We conclude that alemtuzumab is effective for SR-aGVHD in pediatric patients with a tolerable spectrum of complications.

Keywords

steroid-refractory acute graft-versus-host disease; graft-versus-host disease; alemtuzumab; Campath

Acute GVHD is a significant complication of allogeneic HCT and remains a leading cause of morbidity and non-relapse mortality (1, 2). While high dose steroids are the mainstay of

treatment, a variable complete response rate of only 35–70% is observed (2–6). Once deemed steroid refractory, there is no standardized algorithm regarding choice of second-line therapeutic agents (7). While multiple immune suppressive therapies are available, most result in complete response rates of less than 50% and may be accompanied by significant side effects (8–15). Therefore, there is a need to continue to evaluate second-line therapeutic agents for efficacy and complications, especially in the pediatric setting, where studies are often the most limited.

Alemtuzumab (Campath-1H) is a humanized IgG1 monoclonal antibody that targets cells expressing the CD52 antigen, including T-, NK-, and B-lymphocytes and a proportion of monocytes and dendritic cells (16). It is licensed for use in fludarabine-refractory B cell CLL, but has also found a role in T cell tumors in adults and in autoimmune diseases (17, 18). In the allogeneic HCT setting, alemtuzumab is often used as part of reduced intensity conditioning regimens and can decrease the incidence of acute GVHD (19, 20). There are also adult case reports and case series showing the successful use of alemtuzumab for the treatment of SR-aGVHD (21–23). In brief, alemtuzumab therapy has resulted in an overall response rate of 60–80% but with notable rates of infectious complications (24–27). However, to the best of our knowledge, no data describing efficacy or side effect profiles of alemtuzumab in pediatric patients with SR-aGVHD have been published, other than two pediatric patients included in adult series (24, 27).

Here, we report a series of 19 pediatric patients who were treated with alemtuzumab as a single second- or third-line agent for SR-aGVHD. We observed that alemtuzumab led to a complete or partial response in over 70% of patients with a tolerable spectrum of complications and conclude that it is an effective therapeutic modality for pediatric patients.

Patients and methods

Patients

Permission for this retrospective review was granted by the Cincinnati Children's Hospital Medical Center Institutional Review Board. We reviewed the charts of 19 patients diagnosed with SR-aGVHD grades II–IV following allogeneic HCT that were treated with alemtuzumab as a single second- or third-line agent between February 2007 and December 2012. No ongoing or additional research protocols were in effect during the study period for SR-aGVHD in our institution. Allogeneic HCT was performed at Cincinnati Children's Hospital for all except one patient who was referred from an outside center following allogeneic HCT for subsequent management. Patient and transplant characteristics are summarized in Table 1.

Diagnosis of acute GVHD

A clinical diagnosis of acute GVHD was made by the treating physician(s) based on consensus criteria (28) and supported by biopsies whenever clinically indicated. In all cases of GI GVHD, the diagnosis was confirmed by endoscopically obtained tissue biopsies. Skin GVHD was diagnosed by clinical exam only except in one patient who also underwent skin biopsy. Liver GVHD was diagnosed by clinical findings except for one patient who

underwent liver biopsy. The median time to diagnosis or flare of acute GVHD was 60 days after allogeneic HCT (range 23–527 days). Four patients had long-standing GVHD and are reported following an acute flare of their GVHD, as shown in Table 2. SR-aGVHD was defined as progression of acute GVHD after 48 h of ≥ 2 mg/kg methylprednisolone or lack of response after five days of ≥ 2 mg/kg methylprednisolone.

Treatment of acute GVHD prior to alemtuzumab

Patients received a median methylprednisolone dose of 4 mg/kg/day (range 2.5–6 mg/kg/day) for a median duration of eight days (range 3–18 days) prior to receiving alemtuzumab. Additionally, 79% (n = 15) of patients had failed to respond to one or more additional therapeutic agents for SR-aGVHD including sirolimus, mycophenolate mofetil, infliximab, basiliximab, alefacept, abatacept, and photopheresis (Table 2).

Treatment with alemtuzumab

The first or only course of alemtuzumab consisted of a median dose of 0.9 mg/kg (range 0.3–2 mg/kg) administered subcutaneously (n = 14), intravenously (n = 2) or subcutaneously followed by intravenously (n = 3) over 2–6 days at a median of 11 (range 3–72 days) days following the initial diagnosis of acute GVHD or exacerbation of acute GVHD. All patients received premedication with diphenhydramine and acetaminophen (and were receiving methylprednisolone). Treatment courses were repeated in 89% of patients for additional 2–7 courses. For the majority of patients, the first day's dose was 2–3 mg and the subsequent doses did not exceed a daily maximum of 30 mg as per administration guidelines (16). All patients continued receiving their GVHD prophylaxis medications during treatment with alemtuzumab.

Antimicrobial prophylaxis, viral infections, and treatment prior to alemtuzumab

All patients received antimicrobial prophylaxis as per institutional practice against fungi and *Pneumocystis jirovecii*. All patients were receiving viral prophylaxis or indicated antiviral treatment at the time of alemtuzumab. Four patients had asymptomatic CMV viremia at the time of receiving alemtuzumab and were receiving ganciclovir or foscarnet with CMV immune globulin for treatment. One patient had asymptomatic adenoviremia that was being monitored only and remained on prophylactic acyclovir. In addition, one patient had low-level asymptomatic BK viremia, which was being observed. Five patients had a history of infections (herpes zoster, n = 1, treated with acyclovir, respiratory syncytial virus, n = 1, treated with oseltamivir and acyclovir, EBV, n = 2 treated with rituximab and acyclovir, extended spectrum beta lactamase-producing *Escherichia coli* bacteremia treated with systemic antibiotics [n = 1] within the two wk prior to receiving alemtuzumab). The rest (n = 10) had no evidence of viral infections within the two wk prior to alemtuzumab and remained on acyclovir for viral prophylaxis. All patients received intravenous immunoglobulin replacement.

Assessment of response

To assess response to alemtuzumab, we recorded GVHD grade information at the time of alemtuzumab administration, at weekly intervals for four wk following the first

alemtuzumab course and at monthly intervals from four wk to six months following the first alemtuzumab course. A complete response to alemtuzumab was defined as resolution of GVHD, documented by a reduction in the grade of GVHD to zero by four wk after the first dose of alemtuzumab. A partial response was defined as improvement in GVHD by at least one grade at four wk from the first dose of alemtuzumab.

Assessment of relapse of acute GVHD following alemtuzumab

In patients who were observed to have a complete response to alemtuzumab, chart review was performed to record evidence of relapse, defined as reoccurrence of GVHD at any site after achieving a complete resolution (Grade 0).

Development of chronic GVHD

Charts were reviewed for evidence of the development of chronic GVHD.

Adverse effects

Charts were reviewed for evidence of known complications of alemtuzumab including hypersensitivity, rash, fever, thrombocytopenia and neutropenia. Results of clinical microbiologic testing were reviewed for evidence of infectious complications for six months following alemtuzumab, including blood, bronchoalveolar lavage, and tissue cultures and PCRs when applicable, and the results of serial peripheral blood CMV, EBV and adenovirus PCRs, which were performed weekly or twice weekly per routine clinical practice.

Survival

Survival data including date of death and cause of death were collected through the day of last follow-up following the first dose of alemtuzumab. Kaplan–Meier curves were generated with XLSTAT (Addinsoft, Paris, France). Survival was compared between patients who responded to alemtuzumab (complete or partial response) and patients who did not respond, and the p value was calculated using the log rank test. Statistical significance was considered for $p < 0.05$.

Results

Patients

We retrospectively reviewed the charts of 19 pediatric allogeneic stem cell transplant recipients of median age four yr (range 0.5–28 yr) who received alemtuzumab as a single second- or third-line treatment for SR-aGVHD. The underlying indications for allogeneic HCT and details of transplant procedures are shown in Table 1. All patients were HLA typed by molecular methods for eight or 10 alleles (HLA A, B, C, DR, with or without DQ). Over two-thirds of patients ($n = 13$) received a graft from a fully matched unrelated donor (8/8), while the other third received a graft from a single allele mismatched unrelated donor (7/8 or 9/10). Sixteen patients (84%) received bone marrow grafts, two patients received cord blood grafts, and one received peripheral blood stem cells. Thirteen patients (68%) received a reduced intensity conditioning regimen, while the remaining patients (32%)

received a myeloablative conditioning regimen. Twelve patients received alemtuzumab as part of their conditioning regimen, and five patients received antithymocyte globulin.

GVHD grades and organs involved

Grades II, III, and IV SR-aGVHD were observed in three (8%), 10 (52%), and six (31%) patients, respectively (Table 2). Thirty-one percent of patients had GVHD that involved the skin, gastrointestinal tract, and liver. Thirty-one percent of patients had acute GVHD of the skin and gastrointestinal tract. Sixteen percent had isolated skin GVHD, 10% had isolated gastrointestinal tract involvement, 5% had liver and skin involvement, and 5% had liver and gastrointestinal tract involvement.

Prior management

All patients were initially treated with methyl-prednisolone and were receiving a median dose of 4 mg/kg at the time of alemtuzumab (range 2.5–6 mg/kg). All patients had progression of GVHD despite therapy within 48 h or failed to improve within five or more days of receiving 2 mg/kg or greater of steroid therapy. Fifteen patients (79%) had also failed to respond to additional therapeutic agents for SR-aGVHD including sirolimus, mycophenolate mofetil, infliximab, basiliximab, alefacept, abatacept, and photopheresis (Table 2).

Alemtuzumab treatment and response

Alemtuzumab was given as described in the Methods section and as shown in Table 3. The first or only course of alemtuzumab consisted of a median dose of 0.9 mg/kg (range 0.3–2 mg/kg) administered subcutaneously (n = 14), intravenously (n = 2), or subcutaneously followed by intravenously (n = 3) over 2–6 days. A complete response (grade 0) was observed in nine patients (47%) four wk following alemtuzumab (Table 3). A partial response (grade improvement) was observed in five patients (26%). No response was observed in five patients (26%). Twelve patients (63%) were receiving ongoing alemtuzumab therapy at the fourth week when response was measured, and of these patients, five did not demonstrate a response to alemtuzumab and five demonstrated a partial response to alemtuzumab.

Duration of complete responses

Of the nine patients who responded completely to alemtuzumab, three patients (33%) experienced a relapse of acute GVHD within a period of 41–148 days from the first dose of alemtuzumab. These patients were treated with steroids and/or infliximab and again achieved a complete response. The remaining six patients had no relapse of acute GVHD.

GVHD course in patients with partial responses

Of the five patients with partial responses, four patients were additionally treated with other agents within four wk of alemtuzumab (infliximab, basiliximab). Six months following the first dose of alemtuzumab, three of the patients with partial responses had no evidence of GVHD (60%).

GVHD at last follow-up in complete or partial responders

At the time of last follow-up of patients who had experienced a partial or complete response to alemtuzumab, 12 of 14 patients had no evidence of GVHD, while two of 14 had developed chronic GVHD. The median follow-up was 175 days from the first alemtuzumab dose (range 35–1080).

Adverse effects of alemtuzumab

The most common adverse reactions related to alemtuzumab were transient thrombocytopenia in eight patients (42%), fever in seven patients (36%), and transient neutropenia in two patients (10%). Infectious complications that occurred within six months of alemtuzumab are listed in Table 4. Bacteremia with or without sepsis was observed in 47% of patients. CMV viremia was observed in seven patients (36%). One patient developed CMV retinitis, and one patient developed CMV pneumonitis. EBV viremia was observed in seven patients following alemtuzumab (36%). One patient developed EBV related PTLTD 99 days following first alemtuzumab dose. Adenovirus viremia was observed in 10 patients (52%) after alemtuzumab therapy. Two patients developed adenoviral enteritis. Asymptomatic HHV6 viremia occurred in two patients. Hemorrhagic cystitis associated with BK virus was noted in 5% of patients, while asymptomatic BK viremia was noted in 15% of patients. Presumed or documented fungal infections were noted in 21% patients and included central nervous system fungal infection, candidemia, corneal fungal infection, and respiratory fungal infection.

Survival

At six months following the first dose of alemtuzumab, the estimated overall survival was 71% for patients who demonstrated either a partial or complete response to alemtuzumab versus 20% for patients who did not respond (Fig. 1a, $p = 0.026$). Two yr following alemtuzumab, the estimated overall survival of patients who demonstrated a response was 52%, whereas none of the patients who failed to respond were surviving (Fig. 1b, $p = 0.016$). Deaths were due to pneumonia ($n = 1$), chronic idiopathic respiratory failure ($n = 2$), chronic extensive GVHD complicated by bronchiolitis obliterans and respiratory failure ($n = 2$), CMV pneumonitis ($n = 1$), central nervous system presumed fungal infection ($n = 2$), acute hemorrhage ($n = 2$), bacteremia ($n = 1$), and ongoing grade IV acute GVHD ($n = 3$).

Discussion

Historically, patients who do not respond to corticosteroids following five days of treatment are at high risk of death, with mortality rates as high as 50% (2, 6, 29–31). Here, we have demonstrated that alemtuzumab offers an effective therapy for SR-aGVHD in pediatric patients with a notable but tolerable spectrum of complications common to immunosuppressive therapies. We have observed that alemtuzumab results in a grade improvement in over 70% of pediatric patients, with almost 50% of patients experiencing a complete response. The complete response rate is comparable to other commonly used agents for steroid-refractory acute GVHD in children like infliximab, basiliximab, and daclizumab, with complete response rates of 56%, 53%, and 46%, respectively (32–34). The response rates of alemtuzumab are also comparable to those noted in the adult literature,

with overall responses ranging from 50% to 94%, and complete response rates ranging from 20% to 40% (24–27), although some of the adult studies measured responses based on stage improvements as opposed to grade improvements. While limited by heterogeneity in the patient population and the retrospective nature of the study, our experience suggests that alemtuzumab is an effective second- or third-line agent for the treatment of acute steroid-refractory graft-versus-host disease in pediatric patients.

Significant infectious complications were noted following alemtuzumab administration but may have also been influenced by other immune suppressive agents, including high dose steroids. The rates of CMV, EBV, and adenovirus viremias observed in our cohort (36%, 36%, and 52%, respectively) were comparable to our institution's overall incidences following pediatric HCT (20%, 38%, and 53%, respectively) (35). Most infections were managed with antimicrobials effectively, although three patients developed CMV retinitis, CMV pneumonitis, and EBV-associated PTLN. No life-ending complications could be solely attributed to alemtuzumab, but the frequency of infectious complications emphasizes the extent of immunosuppression of this drug. Due to the expected profound lymphocyte depletion, frequent monitoring for infectious complications is vital, as is continuing effective and appropriate antimicrobial prophylaxis.

Of patients who responded to alemtuzumab, the estimated overall two-yr survival was 52%, which is significantly higher than patients who did not respond to alemtuzumab (0%). This is comparable to the observed survival rates in adults ranging from 0 to 54% (24–27). Of the 14 patients that died, a cause directly attributable to acute GVHD or extensive chronic GVHD was observed in three patients who failed to respond to alemtuzumab. Most of the remaining patients died of infectious complications.

Unfortunately, there is no current documentation of an optimal dose and schedule of alemtuzumab for pediatric patients. The initial course of alemtuzumab administered to our patient cohort was heterogeneous, with a median dose of 0.9 mg/kg per course (range 0.2–2 mg/kg per course) given over 2–6 days. Of the patients that responded completely to alemtuzumab, the median initial dose of alemtuzumab received was 1 mg/kg (range 0.6–2 mg/kg) divided over 2–6 days, which is similar to the overall median dose. Several patients received additional courses. Only two patients were treated with a single course of alemtuzumab, with doses of 0.9–1 mg/kg divided over six days. A complete response was observed in these two patients four wk following alemtuzumab, with a later relapse observed in one of them. Our data would suggest that an initial treatment course consisting of a dose of 1 mg/kg alemtuzumab would be a reasonable treatment, pending prospective dose escalation or de-escalation trials. Patients may require further courses to maintain response. Care should be taken with regard to limiting initial doses and cumulative course doses per the manufacturer's recommendations. Additionally, although a threshold for increased infectious death outcome is not known in pediatric patients, dose escalation studies in adults suggest that a threshold likely exists (24, 27). Premedication with acetaminophen and diphenhydramine is suggested, and steroids should also be considered. It may not be necessary to administer additional doses of steroids as premedications; instead, the usual steroid dose as part of GVHD treatment may be timed prior to administration of alemtuzumab. Additionally, subcutaneous administration can decrease reactions (36).

In conclusion, although there are limitations to this study due to a heterogeneous study population and its retrospective nature, alemtuzumab appears to be an effective therapeutic agent for SR-aGVHD in pediatric patients' spectrum. Prospective trials are needed to formally define an optimal dosing schedule of alemtuzumab in this setting.

Acknowledgments

We would like to thank the physicians, nurses, and other providers at Cincinnati Children's Hospital who provided care for the patients, as well as the patients and families themselves.

References

1. Ferrara JL, Levine JE, Reddy P, Holler E. Graft-versus-host disease. *Lancet*. 2009; 373:1550–1561. [PubMed: 19282026]
2. MacMillan ML, Weisdorf DJ, Wagner JE, et al. Response of 443 patients to steroids as primary therapy for acute graft-versus-host disease: Comparison of grading systems. *Biol Blood Marrow Transplant*. 2002; 8:387–394. [PubMed: 12171485]
3. Deeg HJ, Henslee-Downey PJ. Management of acute graft-versus-host disease. *Bone Marrow Transplant*. 1990; 6:1–8. [PubMed: 2202460]
4. Bacigalupo A. Management of acute graft-versus-host disease. *Br J Haematol*. 2007; 137:87–98. [PubMed: 17391488]
5. Van Lint MT, Uderzo C, Locasciulli A, et al. Early treatment of acute graft-versus-host disease with high- or low-dose 6-methylprednisolone: A multicenter randomized trial from the Italian Group for Bone Marrow Transplantation. *Blood*. 1998; 92:2288–2293. [PubMed: 9746766]
6. Van Lint MT, Milone G, Leotta S, et al. Treatment of acute graft-versus-host disease with prednisolone: Significant survival advantage for day +5 responders and no advantage for nonresponders receiving antithymocyte globulin. *Blood*. 2006; 107:4177–4181. [PubMed: 16449522]
7. Deeg HJ, How I. treat refractory acute GVHD. *Blood*. 2007; 109:4119–4126. [PubMed: 17234737]
8. Koreth J, Antin JH. Current and future approaches for control of graft-versus-host disease. *Expert Rev Hematol*. 2008; 1:111. [PubMed: 20151032]
9. Antin JH, Chen AR, Couriel DR, Ho VT, Nash RA, Weisdorf D. Novel approaches to the therapy of steroid-resistant acute graft-versus-host disease. *Biol Blood Marrow Transplant*. 2004; 10:655–668. [PubMed: 15389432]
10. Patriarca F, Sperotto A, Damiani D, et al. Infliximab treatment for steroid-refractory acute graft-versus-host disease. *Haematologica*. 2004; 89:1352–1359. [PubMed: 15531458]
11. Ho VT, Zahrieh D, Hochberg E, et al. Safety and efficacy of denileukin diftitox in patients with steroid-refractory acute graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. *Blood*. 2004; 104:1224–1226. [PubMed: 15113758]
12. Couriel D, Saliba R, Hicks K, et al. Tumor necrosis factor-alpha blockade for the treatment of acute GVHD. *Blood*. 2004; 104:649–654. [PubMed: 15069017]
13. Funke VA, De Medeiros CR, Setubal DC, et al. Therapy for severe refractory acute graft-versus-host disease with basiliximab, a selective interleukin-2 receptor antagonist. *Bone Marrow Transplant*. 2006; 37:961–965. [PubMed: 16565744]
14. Uberti JP, Ayash L, Ratanatharathorn V, et al. Pilot trial on the use of etanercept and methylprednisolone as primary treatment for acute graft-versus-host disease. *Biol Blood Marrow Transplant*. 2005; 11:680–687. [PubMed: 16125638]
15. Toor AA, Stiff PJ, Nickoloff BJ, Rodriguez T, Klein JL, Gordon KB. Alefacept in corticosteroid refractory graft versus host disease: Early results indicate promising activity. *J Dermatolog Treat*. 2007; 18:13–18. [PubMed: 17365261]
16. Campath Prescribing Information. Bayer Health Pharmaceuticals; USA: www.berlex.com/html/products/pi/Campath_PI.pdf

17. Reiff A, Shaham B, Weinberg KI, Crooks GM, Parkman R. Anti-CD52 antibody-mediated immune ablation with autologous immune recovery for the treatment of refractory juvenile polymyositis. *J Clin Immunol*. 2011; 31:615–622. [PubMed: 21541793]
18. Kluin-Nelemans HC, Van Marwijk Kooy M, Lugtenburg PJ, et al. Intensified alemtuzumab-CHOP therapy for peripheral T-cell lymphoma. *Ann Oncol*. 2011; 22:1595–1600. [PubMed: 21212158]
19. Kottaridis PD, Milligan DW, Chopra R, et al. In vivo CAMPATH-1H prevents graft-versus-host disease following nonmyeloablative stem cell transplantation. *Blood*. 2000; 96:2419–2425. [PubMed: 11001893]
20. Sorror ML, Maris MB, Storer B, et al. Comparing morbidity and mortality of HLA-matched unrelated donor hematopoietic cell transplantation after nonmyeloablative and myeloablative conditioning: Influence of pretransplantation comorbidities. *Blood*. 2004; 104:961–968. [PubMed: 15113759]
21. Carella AM, Beltrami G, Scalzulli PR, Carella AM Jr, Corsetti MT. Alemtuzumab can successfully treat steroid-refractory acute graft-versus-host disease (aGVHD). *Bone Marrow Transplant*. 2004; 33:131–132. [PubMed: 14566330]
22. Wandroo F, Auguston B, Cook M, Craddock C, Mahendra P. Successful use of Campath-1H in the treatment of steroid refractory liver GvHD. *Bone Marrow Transplant*. 2004; 34:285–287. [PubMed: 15170160]
23. Busca A, Locatelli F, Lovisone E, et al. Treatment of severe refractory acute graft-versus-host disease of the gastrointestinal tract with Campath-1H. *Biol Blood Marrow Transplant*. 2005; 11:734–736. [PubMed: 16125645]
24. Gomez-Almaguer D, Ruiz-Arguelles GJ, Del Carmen Tarin-Arzaga L, et al. Alemtuzumab for the treatment of steroid-refractory acute graft-versus-host disease. *Biol Blood Marrow Transplant*. 2008; 14:10–15. [PubMed: 18158956]
25. Martinez C, Solano C, Ferra C, Sampol A, Valcarcel D, Perez-Simon JA. Alemtuzumab as treatment of steroid-refractory acute graft-versus-host disease: Results of a phase II study. *Biol Blood Marrow Transplant*. 2009; 15:639–642. [PubMed: 19361757]
26. Schnitzler M, Hasskarl J, Egger M, Bertz H, Finke J. Successful treatment of severe acute intestinal graft-versus-host resistant to systemic and topical steroids with alemtuzumab. *Biol Blood Marrow Transplant*. 2009; 15:910–918. [PubMed: 19589480]
27. Schub N, Gunther A, Schrauder A, et al. Therapy of steroid-refractory acute GVHD with CD52 antibody alemtuzumab is effective. *Bone Marrow Transplant*. 2011; 46:143–147. [PubMed: 20348971]
28. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant*. 1995; 15:825–828. [PubMed: 7581076]
29. Roy J, McGlave PB, Filipovich AH, et al. Acute graft-versus-host disease following unrelated donor marrow transplantation: Failure of conventional therapy. *Bone Marrow Transplant*. 1992; 10:77–82. [PubMed: 1515883]
30. Westin JR, Saliba RM, De Lima M, et al. Steroid-refractory acute GVHD: Predictors and outcomes. *Adv Hematol*. 2011; 2011:601953. [PubMed: 22110505]
31. Pasquini MC. Impact of graft-versus-host disease on survival. *Best Pract Res Clin Haematol*. 2008; 21:193–204. [PubMed: 18503986]
32. Sleight BS, Chan KW, Braun TM, Serrano A, Gilman AL. Infliximab for GVHD therapy in children. *Bone Marrow Transplant*. 2007; 40:473–480. [PubMed: 17618323]
33. Massenkeil G, Rackwitz S, Genvresse I, Rosen O, Dorken B, Arnold R. Basiliximab is well tolerated and effective in the treatment of steroid-refractory acute graft-versus-host disease after allogeneic stem cell transplantation. *Bone Marrow Transplant*. 2002; 30:899–903. [PubMed: 12476283]
34. Miano M, Cuzzubbo D, Terranova P, et al. Daclizumab as useful treatment in refractory acute GVHD: A paediatric experience. *Bone Marrow Transplant*. 2009; 43:423–427. [PubMed: 18850021]
35. Ozdemir N, Jodele S, Myers K, et al. Prevalence of viral infections in children undergoing first allogeneic hematopoietic stem cell transplantation: Two year single center experience. *Biol Blood Marrow Transplant*. 2012; 18:S315–S316.

36. Lundin J, Kimby E, Bjorkholm M, et al. Phase II trial of subcutaneous anti-CD52 monoclonal antibody alemtuzumab (Campath-1H) as first-line treatment for patients with B-cell chronic lymphocytic leukemia (B-CLL). *Blood*. 2002; 100:768–773. [PubMed: 12130484]

Abbreviations

CMV	cytomegalovirus
EBV	Epstein–Barr virus
GVHD	graft-versus-host disease
HCT	hematopoietic cell transplantation
HLA	human leukocyte antigen
PTLD	post-transplant lymphoproliferative disease
SR-aGVHD	steroid-refractory acute graft-versus-host disease

Fig. 1.

(a) Survival at six months based on response to alemtuzumab. (b) Survival at two yr based on response to alemtuzumab.

Table 1

Patient demographics

Patient	Age in years	Diagnosis	Match (HLA A, B, zC, DR, DQ)	Relation	Source	Preparative regimen	GVHD prophylaxis
1	0.5	FHLH [*]	7 of 8	Unrelated	Bone marrow	Alentuzumab, fludarabine, melphalan	Cyclosporine, methylprednisolone
2	0.6	SCID [†]	8 of 8	Unrelated	Bone marrow	Alentuzumab, fludarabine, melphalan	Cyclosporine, methylprednisolone
3	0.97	Wiskott-Aldrich syndrome	8 of 8	Unrelated	Bone marrow	Busulfan, cyclophosphamide, ATG [‡]	Cyclosporine, methylprednisolone
4	0.98	HLH	5 of 6	Unrelated	Bone marrow	Alentuzumab, fludarabine, melphalan	Cyclosporine, methylprednisolone, methotrexate
5	1.5	Hurler's syndrome	5 of 6	Unrelated	Cord blood	Alentuzumab, fludarabine, melphalan	Cyclosporine, methylprednisolone
6	1.8	Acute myeloid leukemia	5 of 6	Unrelated	Cord blood	Busulfan, cyclophosphamide, ATG	Cyclosporine, methylprednisolone
7	1.9	Hurler's syndrome	8 of 8	Unrelated	Bone marrow	Alentuzumab, fludarabine, melphalan	Cyclosporine, methylprednisolone, methotrexate
8	2	LCH [§]	8 of 8	Unrelated	Bone marrow	Alentuzumab, fludarabine, melphalan	Tacrolimus, methylprednisolone
9	2	FHLH	7 of 8	Unrelated	Bone marrow	Alentuzumab, fludarabine, melphalan	Cyclosporine, methylprednisolone
10	4	FHLH	8 of 8	Unrelated	Bone marrow	Alentuzumab, fludarabine, melphalan	Cyclosporine, methylprednisolone
11	4.7	Relapsed T cell ALL [¶]	8 of 8	Unrelated	Bone marrow	TBI ^{**} , thiotepe, cyclophosphamide	Sirolimus, tacrolimus
12	5.4	Aplastic anemia	8 of 8	Unrelated	Bone marrow	Alentuzumab, fludarabine, melphalan	Cyclosporine, methylprednisolone
13	7.4	CID ^{‡‡}	7 of 8	Unrelated	PBSC ^{‡‡}	Alentuzumab, fludarabine, melphalan	Cyclosporine, methylprednisolone, methotrexate
14	9.2	Wiskott-Aldrich syndrome	8 of 8	Unrelated	Bone marrow	Busulfan, cyclophosphamide, ATG	Cyclosporine, methylprednisolone
15	10	Chronic myeloid leukemia	9 of 10	Unrelated	Bone marrow	Busulfan, cyclophosphamide, ATG	Cyclosporine, methotrexate
16	10.2	Aplastic anemia	8 of 8	Unrelated	Bone marrow	Alentuzumab, fludarabine, melphalan	Cyclosporine, methylprednisolone
17	17.9	Chronic myeloid leukemia	8 of 8	Unrelated	Bone marrow	TBI, cyclophosphamide, ATG	Cyclosporine, methotrexate
18	18.7	Chronic myeloid leukemia	8 of 8	Unrelated	Bone marrow	Alentuzumab, fludarabine, melphalan	Cyclosporine, methylprednisolone
19	28	MDS ^{§§} Monosomy 7	8 of 8	Unrelated	Bone marrow	Fludarabine, melphalan	Mycophenolate mofetil, methylprednisolone

* Familial hemophagocytic lymphohistiocytosis.

† Severe combined immune deficiency.

‡ Antithymocyte globulin.

§ Langerhan's cell histiocytosis.

¶ Acute lymphoblastic leukemia.

** Total body irradiation.

^{††} Combined immune deficiency.

^{‡‡} Peripheral blood stem cells.

^{§§} Myelodysplastic syndrome.

Table 2
GVHD characteristics and steroid treatment prior to alemtuzumab

Patient	Diagnosis of GVHD from day of transplant (days)	DLI given	Duration of acute GVHD or GVHD exacerbation* (time since original acute GVHD diagnosis)	Involved site(s)	Consecutive days of 2 mg/kg steroid treatment	Additional therapeutic agents given prior to alemtuzumab	Actual dose of alemtuzumab in mg
1	141	Yes	24 days	Skin, liver	18	None	2
2	38	No	9 days	Skin, GI [†] , liver	5	Basiliximab	6
3	49	No	10* days (1.5 yr)	GI	6	Infliximab, abatacept, sirolimus	13
4	266	Yes	7* days (1 yr)	Skin, GI	4	None	7.2
5	39	No	11 days	Skin	9	Abatacept	19
6	26	No	3 days	GI	3	None	13.2
7	38	No	18 days	Skin, GI	15	Infliximab, MMF*	15
8	527	No	11 days	Skin	8	None	13
9	60	No	5* days (56 days)	Skin, GI	5	Infliximab	15
10	64	Yes	10 days	Skin, GI, liver	9	Basiliximab, infliximab	27
11	78	No	72 days	GI, liver	12	Basiliximab, infliximab	18
12	74	No	5 days	Skin, GI, liver	5	Infliximab	15
13	181	Yes	49 days* (97 days)	Skin	17	Alefacept, basiliximab, photopheresis	18
14	36	No	8 days	Skin, GI, liver	8	Infliximab	40
15	49	No	11 days	Skin, GI	11	Basiliximab	25
16	23	No	12 days	Skin, GI	12	Infliximab	53
17	60	No	5 days	Skin, GI, liver	5	Infliximab	43
18	95	Yes	15 days	Skin, GI	11	Infliximab	53
19	27	No	3 days	Skin, GI, liver	3	Infliximab	53

* Mycophenolate mofetil.

[†] Gastrointestinal tract.

Table 3
Alemtuzumab dose, grades of GVHD before and after alemtuzumab, steroid doses before and four wk after alemtuzumab, and novel agents added and responses in patients

Patient	Alemtuzumab dose, mg/kg (first or only course)	Acute GVHD grade prior to alemtuzumab	Acute GVHD grade four wk Post-Alemtuzumab	Steroid dose, mg/kg/day at start of alemtuzumab	Steroid dose, mg/kg/day, four wk Following first or only alemtuzumab course	Novel agents added three or four wk following alemtuzumab	Complete, partial, or no response
1	0.3	3	2	5	3	None	PR
2	1	3	1	2.5	2.25	None	PR
3	1.1	3	0	5	2	None	CR
4	0.6	4	0	4	2	None	CR
5	2	4	0	6	2	None	CR
6	1	3	0	6	2	None	CR
7	1	4	4	4	1.5	Basiliximab	NR
8	0.65	2	0	6	3.5	None	CR
9	1	2	0	4	1.8	None	CR
10	1	3	0	4	1.8	Interleukin 2	CR
11	0.8	3	3	2.5	0.8	None	NR
12	1	2	1	4	2	None	PR
13	0.7	4	4	3	6.2	Infliximab	NR
14	0.8	4	3	4	2.5	None	PR
15	1	3	2	3	2	Infliximab	PR
16	1	3	0	4	2	None	CR
17	0.6	3	4	4	2.5	None	NR
18	0.9	4	0	4	2	None	CR
19	0.7	3	4	4	1.5	None	NR

NA, not applicable.

Table 4
Infectious complications observed within six months of the first or only alemtuzumab course

Infectious complication	Number of patients with detection of organism (%)	Number of patients with symptomatic disease (%)
Bacteremia	9 (47)	9 (47)
Fungal infection	4 (21)	4 (21)
CMV viremia [*]	7 (36)	2 (10)
EBV viremia [†]	7(36)	1(5)
Adenovirus viremia [‡]	10 (52)	2 (10)
HHV6 viremia [§]	2 (10)	0
BK viremia [¶]	3 (15)	1 (5)

^{*}Two wk prior to alemtuzumab, four patients had detectable CMV viremia (21%).

[†]Two wk prior to alemtuzumab, three patients had detectable EBV viremia (16%).

[‡]Two wk prior to alemtuzumab, one patient had detectable adenovirus viremia (5%).

[§]Two wk prior to alemtuzumab, zero patients had detectable HHV6 viremia. (0%).

[¶]Two wk prior to alemtuzumab, one patient had detectable BK viremia (5%).