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Salvage Therapy of Refractory Hemophagocytic Lymphohistiocytosis with Alemtuzumab

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Abstract

Background—Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome that remains difficult to treat. Even with current standard HLH therapy, only approximately half of patients will experience complete resolution of disease, and early mortality remains a significant problem. Salvage therapies have been described only in limited case reports, and there are no large studies of second-line therapies.

Procedure—We reviewed the charts of 22 pediatric and adult patients who received alemtuzumab for the treatment of refractory HLH at our center or in consultation with our group.

Results—Patients had received conventional therapies for a median of 8 weeks (range 2–70) prior to alemtuzumab, and treatment immediately prior to alemtuzumab included dexamethasone (100%), etoposide (77%), cyclosporine (36%), intrathecal hydrocortisone +/- methotrexate (23%), methylprednisolone (9%), and rituximab (14%). Patients received a median dose of 1mg/kg alemtuzumab (range 0.1–8.9mg/kg) divided over a median of 4 days (range 2–10). Fourteen

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Conflict of Interest

The authors declare that there are no conflicts of interest.

Author Contributions

R.A.M. designed research, collected and analyzed data, and wrote the manuscript. C.E.A., K.L.M., J.L.W., J.K.W., J.S., N.D.L., S.P.K., and J.J.B. collected data and edited the manuscript. J.L. collected pharmacologic data and edited the manuscript. J.M. reviewed pathology and edited the manuscript. A.H.F. designed research and edited the manuscript. M.B.J. designed research, analyzed data, wrote portions of the manuscript, and edited the manuscript.

patients experienced an overall partial response, defined as at least a 25% improvement in 2 or more quantifiable symptoms or laboratory markers of HLH 2 weeks following alemtuzumab (64%). Five additional patients had a 25% or greater improvement in a single quantifiable symptom or laboratory marker of HLH (23%). Seventy-seven percent of patients survived to undergo allogeneic hematopoietic cell transplantation. Patients experienced an acceptable spectrum of complications, including CMV and adenovirus viremia.

Conclusion—Alemtuzumab appears to be an effective salvage agent for refractory HLH, leading to improvement and survival to HCT in many patients. Prospective trials to define optimal dosing levels, schedules, and responses are needed.

Keywords

Alemtuzumab; Campath; Hemophagocytic Lymphohistiocytosis; HLH

Introduction

HLH is a severe immune dysregulatory disorder manifested by overwhelming and life-threatening immune activation. Despite improvements in standard-of-care therapies over the last 15 years, HLH is often refractory to treatment and poses a significant risk of death.

For most patients, the standard treatment of HLH consists of dexamethasone and etoposide, with or without cyclosporine. [1,2] Approximately 80% of patients will respond to these therapies and survive to hematopoietic cell transplantation (HCT), but complete responses are only achieved in approximately half of patients. [1] The majority of deaths prior to HCT appear to be due to uncontrolled disease activity. [1] An alternative treatment regimen, consisting of steroids, cyclosporine, and anti-thymocyte globulin, has been shown to result in a higher initial complete response rate of 73%. [3] However, early relapse was common with this regimen, and death prior to HCT occurred in approximately one quarter of patients. [3] Of note, in patients who survive to HCT, poor HLH control is associated with higher transplant-related mortality, [4–6] which further underscores the need for effective second-line or “salvage” therapies.

There is a paucity of literature to guide physicians regarding choice of therapy for patients with refractory HLH. Infliximab, anakinra, alemtuzumab, daclizumab, vincristine, and other therapies have been reported in a limited number of cases, [7–12] but there are no large retrospective or prospective studies.

The ideal second-line therapy would provide robust suppression of multiple arms of the immune response, including cytotoxic effector CD8+ T cells and NK cells, cytokine-producing CD4+ T cells, and antigen presenting cells including macrophages and dendritic cells. Alemtuzumab is a therapeutic monoclonal antibody directed against the CD52 antigen, a small GPI-anchored protein which is expressed on lymphocytes including T cells, NK cells, and B cells, as well as many monocytes, macrophages, and dendritic cells. [13–15] Alemtuzumab quickly and efficiently depletes CD52-expressing cells, which makes it an attractive agent for the treatment of refractory HLH. Indeed, alemtuzumab has been described as a successful bridge to HCT in 1 patient. [9] Additionally, alemtuzumab is commonly used as part of reduced-intensity conditioning (RIC) HCT regimens, which have significantly improved the survival of patients with HLH, possibly due in part to the inclusion of this drug. [16–18]

Due to the critical role of lymphocytes in HLH pathogenesis [19] and the early successes of alemtuzumab, we have used alemtuzumab for the treatment of pediatric and adult patients with refractory HLH. Here we describe our experience.

Methods

Patients and Diagnosis of Refractory HLH

Permission for this retrospective review was granted by the Cincinnati Children's Hospital Medical Center, Texas Children's Hospital, and Riley Hospital for Children Institutional Review Boards. We reviewed the charts of patients with refractory HLH treated with alemtuzumab between 2004 and September, 2010. All patients met clinical criteria for the diagnosis of HLH as defined by the Histiocyte Society upon initial clinical presentation, as summarized in Supplemental Table I. Patients were treated with alemtuzumab at our center or in collaboration with our center.

There are no accepted diagnostic criteria for refractory HLH. Patients were diagnosed with refractory HLH based on persistent or worsening symptoms and laboratory markers of HLH despite standard HLH therapies by their primary treating physicians. Charts were reviewed for the presence of the diagnostic symptoms and laboratory markers of HLH that were present at the time of alemtuzumab. Patients were included in this review if there was documentation of elevated levels of soluble IL-2 receptor and/or ferritin at the time of alemtuzumab, with or without hypertriglyceridemia, and at least one or more of the following: anemia, neutropenia, thrombocytopenia, hepatosplenomegaly, hemophagocytosis (observed in a biopsy specimen within 1 month of alemtuzumab), transaminitis with an ALT greater than 400 in the absence of a more likely cause of transaminitis other than HLH (not a diagnostic criteria, but often observed in patients with HLH), or altered level of consciousness due to central nervous system HLH. Fibrinogen was not checked consistently in patients, and information regarding fever was difficult to review due to lack of temperature recordings or due to inability to discern the source of fever, so these criteria were not analyzed. Detailed case reports for each patient are summarized in the Supplemental Materials.

HLH Treatment Prior to Alemtuzumab

Charts were reviewed to determine the overall length of HLH treatment and the specific treatment received within the 2 weeks prior to alemtuzumab.

Anti-microbial Prophylaxis and Treatment

Before and after treatment, all patients received anti-microbial prophylaxis, most commonly including pentamidine or co-trimoxazole; voriconazole, amphotericin, or caspofungin; and acyclovir. Patients received immunoglobulin replacement to maintain serum IgG levels well within the normal range. Active infections were treated as clinically indicated.

Assessment of Response

We reviewed charts and recorded quantifiable symptoms and laboratory markers of HLH at weekly intervals through week 4 following alemtuzumab. Information recorded included: levels of soluble IL-2 receptor, ferritin, and triglyceride; hemoglobin, neutrophil counts, platelet counts, ALT, level of consciousness (documented in clinical exams in patients with CNS HLH), and presence of hemophagocytosis in pathology specimens.

A complete response was defined as normalization of all of the above quantifiable symptoms and laboratory markers of HLH. A partial response was defined as at least a 25% improvement in 2 or more quantifiable symptoms and laboratory markers by 2 weeks following alemtuzumab as follows. Soluble IL-2 receptor response was defined as a greater than a 1.5 fold decrease. Ferritin and triglyceride responses were defined as decreases of at least 25%. Responses based on hemoglobin or platelet counts were not able to be determined due to transfusions. For patients with an initial ANC of less than 500, a response was

defined as an increase of ANC by at least 100% to greater than 500 cells/mcL. For patients with an ANC 500–2000 cells/mcL, an increase by at least 100% to more than 5000 cells/mcL was considered a response. For patients with transaminitis with an ALT greater than 400, an ALT response was defined as a decrease of ALT of at least 50%. For patients with hemophagocytosis noted on a biopsy specimen within 4 weeks of alemtuzumab, a response was defined as resolution of hemophagocytosis following alemtuzumab. For patients with refractory CNS HLH and altered level of consciousness, a response was defined as a normal level of consciousness following alemtuzumab. For patients who died or started preparative regimens for HCT within 14 days of alemtuzumab, the last known values were used as day 14 laboratory results.

Diagnostic criteria not utilized in assessment of response included fibrinogen, as this was not checked consistently in patients; fever, because information was often lacking or difficult to interpret; and liver and spleen size, as examinations and imaging results were not consistently documented. Cerebrospinal fluid testing results were not analyzed in patients with CNS HLH because sampling was inconsistent.

Toxicities and Complications

Charts were reviewed for evidence of hypersensitivity to alemtuzumab or evidence of worsening cytopenias as a result of alemtuzumab. Toxicities were graded using The Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events v4.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Results of clinical microbiologic testing were reviewed for evidence of infectious complications.

Survival

We collected survival data including survival to allogeneic HCT, survival to day +100 following HCT, and total survival time (at last follow up) or time to death. The Kaplan-Meier survival curve was generated using XLSTAT software (Addinsoft).

Results

Patients

Twenty-two patients were diagnosed with refractory HLH by their primary physicians after failing to achieve an adequate response to initial or re-intensified HLH therapy, or were unable to tolerate full re-intensification of etoposide therapy (Table I). The median time between the initiation of therapy and the diagnosis of refractory HLH was 8 weeks (range 2–70 weeks). During the 2 weeks immediately prior to alemtuzumab, treatments included dexamethasone, etoposide, cyclosporine, and intrathecal hydrocortisone +/- methotrexate in 100%, 77% (all had received etoposide previously), 36%, and 23% of patients, respectively (Table I). Two patients also received methylprednisolone, and 3 patients received rituximab. One patient uniquely received Ara-C as part of a HCT preparative regimen, which was subsequently held due to gastrointestinal bleeding, critical status, and worsening of HLH which lead to alemtuzumab salvage.

The manifestations of refractory HLH are summarized in Table II, and case summaries for each patient are available online as supplemental information. Fourteen of 18 patients (78%) who received testing of soluble IL-2 receptor levels had elevated levels. Ferritin levels were available for 21 patients and all but 1 patient had an elevated ferritin, with a median ferritin of 4861 ng/mL (range 237–174,119 ng/mL). All patients were cytopenic in one or more lineages, with a median absolute neutrophil count (ANC) of 231 cells/mcL and a median platelet count of 47,500/mcL on the first day of alemtuzumab. Fifteen patients were requiring blood and/or platelet transfusions. Fourteen patients had hepatomegaly and/or

splenomegaly. Seventeen patients had bone marrow, liver, lung, or lymph node biopsies within 1 month prior to alemtuzumab, and 12 patients (71%) were observed to have hemophagocytosis. Four patients had an elevation of ALT >400 due to HLH. Two patients had refractory symptomatic CNS HLH manifested by altered levels of consciousness.

Alemtuzumab Treatment

There was no precedent for treating HLH with alemtuzumab. Patients received alemtuzumab based on one of two dosing schedules used in conditioning regimens for HCT. Thirteen patients received a dose escalation schedule. [20] Ten of these patients received an initial 3–5mg dose followed by 5–30mg per dose daily over 4 days. Three patients received a dose escalation schedule administered over 2–8 days. A second alemtuzumab dosing schedule was used for 4 patients and given as 1mg/kg divided over 4–6 days. [16] The remaining 5 patients received modified individualized dosing schedules, with 0.14–2.4mg/kg administered over 2–10 days. Doses were administered intravenously (n=7), subcutaneously (n=14), or both (n=1). Overall, the median alemtuzumab dose given to patients was 1mg/kg (range 0.1–8.9mg/kg) divided over a median of 4 days (range 2–10 days) as a first or only course (Table III). Eleven patients received 1 or more additional courses of alemtuzumab.

Response

Decreases of absolute lymphocyte counts (ALCs) were readily observed (Figure 1A). Increases in absolute neutrophil counts (ANCs) were observed in 13 out of 17 patients (76%) who demonstrated ANCs less than 2000 cells/mcL on the day of alemtuzumab (Table III and Figure 1B). Fourteen of these patients had ANCs of 0–420 cells/mcL prior to alemtuzumab, and in 11 patients the ANC rose to 820–15,750 cells/mcL 2 weeks following alemtuzumab. Hemoglobin and platelet responses were not evaluable due to transfusions in the majority of patients. All 4 patients with ALTs ranging from 474–1893 unit/L had a greater than 50% decrease in the ALT following alemtuzumab (100% response). The ALTs decreased to 54–794 unit/L (Table III and Figure 1C).

Decreases in levels of inflammatory markers of HLH were observed in the majority of evaluable patients. Of 15 evaluable patients with a ferritin of 1000ng/mL or greater prior to alemtuzumab, 10 patients were observed to have at least a 25% decrease in ferritin 2 weeks following alemtuzumab (67% response) (Table III and Figure 1D), and 7 of these patients had a 50–93% decrease in ferritin. The median ferritin for this group decreased from 9021 ng/mL (range 1360–174,119 ng/mL) to 5010 ng/mL (range 944–19030 ng/mL). Of 9 evaluable patients with an elevated soluble IL-2 receptor prior to alemtuzumab, 7 patients were observed to have a 1.6–4 fold decrease 2 weeks following alemtuzumab (78% response) (Table III and Figure 1E). Of 10 evaluable patients with an elevated triglyceride level prior to alemtuzumab, 7 were observed to have a decrease of 28–63% 2 weeks following alemtuzumab (70% response) (Table III and Figure 1F).

For patients 17 and 18, whose principal quantifiable indications of refractory HLH were persistent hemophagocytosis +/- thrombocytopenia (in addition to elevation of inflammatory markers of HLH), a bone marrow biopsy performed 1 week following alemtuzumab in patient 17 showed disappearance of hemophagocytosis. No repeat bone marrow biopsy was performed for patient 18.

Follow up of patients with refractory CNS disease was limited because post-treatment cerebrospinal fluid (CSF) was not available in patients 7 and 19. There was a lack of adequate data to fully comment on the responsiveness of refractory CNS disease to alemtuzumab in these patients, other than the observation that no significant clinical

improvement was noted on clinical examinations, though patient 19 died soon after alemtuzumab.

Overall, no patient experienced a complete response to alemtuzumab therapy. Fourteen of 22 patients had a response in 2 or more quantifiable symptoms or laboratory markers of HLH and thus an overall partial response (64%) (Table III). Five additional patients had an isolated improvement in 1 quantifiable symptom or laboratory marker of HLH (23%) (Table III). Patients with an elevated soluble IL-2 receptor and a ferritin greater than 2000ng/mL trended to have a higher partial response rate. Of 8 such patients (patients 1, 4, 11, 15, 19, 20, 21, and 22), 6 had a partial response (75%). There was no correlation of response with the presence of a genetically identified disease. Of the 6 patients with a genetic diagnosis, 4 experienced an overall partial response (67%), which is similar to the total percentage of partial responders (64%).

Durability of Response

The durability of response for a single course of alemtuzumab was evaluable in only 3 patients because most patients received (an) additional course(s) of alemtuzumab (n=11), received additional salvage therapies (n=2), died (n=3), or began HCT conditioning regimens (n=7) within 28 days following alemtuzumab. In these three patients we observed the following. Patient 14 received salvage therapy with an ANC of 0. Following alemtuzumab, this patient recovered normal neutrophil counts and maintained them until HCT 57 days later without acute worsening of HLH or further salvage therapy (Figure 2A). Patient 4 received alemtuzumab with an ANC of 70. This patient initially responded to alemtuzumab with an improvement in ANC, but after 3 weeks the ANC decreased to less than 500 (Figure 2B). A second course of alemtuzumab was administered 29 days following the initial course, and again improved the ANC to greater than 1000 which was maintained until HCT 99 days following the initial alemtuzumab (Figure 2B). Patient 6 received alemtuzumab salvage therapy predominantly for refractory hepatitis. Alemtuzumab resulted in a remarkable decrease in the ALT, but after 4 weeks the ALT again began to rise. A second course of alemtuzumab was administered 33 days following the first dose, which again resulted in improvement of the ALT (Figure 2C). It is notable that following the second course, the ALT began to climb 2 weeks later, and alemtuzumab administered as part of the patient's HCT conditioning regimen resulted in improvement (Figure 2C).

Toxicities

There were a limited number of alemtuzumab-related adverse events. Four patients were noted to have a possible grade 1 hypersensitivity reaction characterized by fever, though it is unclear if the fever was due to alemtuzumab or to another cause. One patient experienced a grade 2 hypersensitivity reaction characterized by urticaria. Grade 3 transient worsening of neutropenia was observed in 4 patients, and grades 1–2 transient worsening of thrombocytopenia was observed in 2 patients.

Infections

Nine patients experienced bacteremia or candidemia within the 2 months following alemtuzumab. CMV and adenovirus viremias were common. CMV was detected in whole blood in 14% of patients before alemtuzumab, and 32% following alemtuzumab. Detection of adenovirus in the blood increased from 0% prior to alemtuzumab, to 23% following alemtuzumab. The incidence of EBV viremia was essentially unchanged following alemtuzumab, detected in 36% of patients prior to alemtuzumab versus 23% of patients following alemtuzumab. No patients displayed evidence of EBV driven lymphoproliferative disease.

Survival

Four patients died prior to HCT at a median of 14 days following alemtuzumab (range 10–262 days) (Supplemental Table II and Figure 3A). Three of these patients were critically ill with 1 or more organ failures prior to alemtuzumab, and died 10–16 days following alemtuzumab due to gastrointestinal bleeding, intracranial bleeding, infections with multiple organisms including EBV, Herpes simplex virus, Varicella Zoster, sepsis (with Enterococcus, Escherichia coli, or Stenotrophomonas maltophilia), and organ/multi-organ failure (including respiratory failure, renal failure, and cardiac dysrhythmia). The fourth patient suffered severe central nervous system compromise due to CNS HLH, was tracheostomy and ventilator dependent, and died 262 days following alemtuzumab with ongoing HLH, infectious complications, and organ failure.

Seventeen patients (77%) survived to undergo allogeneic HCT at a median of 52 days following first alemtuzumab administration (range 16–121 days) (Supplemental Table II and Figure 3A). One additional patient is surviving and not currently a candidate for HCT due to severe deconditioning (bed-bound) and decubitus ulceration, and has continued HLH therapy while undergoing rehabilitation. All but 1 patient undergoing HCT survived to day +100 following HCT. Overall long-term probability of survival of patients following salvage therapy with alemtuzumab is 64% (+/– 21%) at a median of 870 days following first alemtuzumab administration (range 459–2142 days) (Figure 3B).

Discussion

Here we have documented the outcomes of 22 patients who received alemtuzumab for salvage therapy of refractory HLH. Sixty-four percent of patients experienced an overall partial response following alemtuzumab treatment as defined as a 25% or greater improvement in 2 or more quantifiable symptoms or laboratory markers of HLH. Additional patients experienced an improvement in a single quantifiable symptom or laboratory marker of HLH. No complete responses were observed. However, the ability to gauge a complete response was hindered by the fact that many patients received additional courses of alemtuzumab or moved quickly to HCT, in which case the monitoring period was likely too short to allow a full recovery from HLH since complete responses often take many weeks to be manifest with conventional therapy. Though no complete responses were observed, the high response and survival rates observed in this very challenging patient population suggest that alemtuzumab has significant activity in treating refractory HLH.

Because many patients received additional courses of alemtuzumab or moved quickly to HCT, it was not possible to judge the duration of response to alemtuzumab. However, it is notable that patients 4 and 6 who each received a second course of alemtuzumab at 29 and 33 days following the initial treatment course, did so due to worsening of HLH symptoms at those times. Given the fact that the median time of response of ATG was previously observed to be 1.3 months, [3] alemtuzumab may have a similar duration of response. Patient 14's response to alemtuzumab lasted until HCT 57 days later, which does suggest that some patients may experience a durable response to 1 course.

The most significant benefit of alemtuzumab therapy appears to be the high rate of survival to HCT. While survival of patients with refractory HLH is not clearly described in the literature, clinical experience strongly suggests that patients who fail to respond adequately to conventional therapies have very poor survival. In this series, treatment with alemtuzumab allowed 77% of patients with refractory HLH to survive until HCT, and 1 additional patient is currently surviving without undergoing HCT.

The number of patients who proceeded to allogeneic HCT in our series is high. In part this reflects the consensus that patients with refractory and/or recurrent HLH are likely to have a familial/genetic disease etiology (even if a genetic lesion is not identified). However, the decision to pursue allogeneic HCT in patients with refractory HLH who respond to alemtuzumab should be made on an individual basis. Physicians should consider the patient's genetic work-up, results of NK cell and T cell functional cytotoxicity and degranulation studies, previous clinical course, and the likelihood of remaining in remission following alemtuzumab.

Patients tolerated alemtuzumab with only modest acute complications. A minority of patients experienced fever or urticaria, or transiently worsened cytopenias. There were no cases of severe hyperinflammatory response or anaphylaxis. The rate of hypersensitivity reactions may be low in our patients due to our practice to administer alemtuzumab subcutaneously, which may limit reactions, [21] and to pre-medicate patients with acetaminophen, diphenhydramine, and steroids.

The most significant complication of alemtuzumab was the development of CMV and/or adenovirus viremia, which each occurred in approximately ¼ of patients. This is similar to the rates of viremias observed in patients undergoing allogeneic HCT with a reduced-intensity conditioning protocol that includes alemtuzumab, [18] and CMV reactivation is known to occur following alemtuzumab treatment in other clinical settings as well.

Three deaths occurred within 2 weeks of alemtuzumab. Deaths were secondary to multiple causes, including active viral infections which could have been exacerbated by alemtuzumab-mediated lymphocyte depletion. However, given the critical nature of the patients' conditions and pre-existing organ failure prior to alemtuzumab, it is difficult to determine causality.

Overall, we conclude that alemtuzumab may be an effective salvage agent with acceptable toxicity for some patients with refractory HLH. We would suggest that such salvage therapy be considered in patients who do not manifest improvements in clinical indices and who display persistently elevated inflammatory markers after 2–4 weeks of conventional or re-intensified therapy. In our experience, delays beyond this timeframe are likely to lead to critical illness and poor outcomes regardless of the salvage strategy utilized.

Unfortunately, there are no clear data regarding the optimal timing and dose of alemtuzumab. We observed clinical activity with a wide range of doses and no correlation was observed between dose and outcomes. A prospective trial is needed to define optimal dosing levels, dosing schedules, and responses. Until better data are available, a reasonable approach would be to use the median dose received by patients in this cohort (1mg/kg), with the total dose capped for larger patients per the published manufacturer's recommendations. This dose is similar to that used in HCT regimens. The dose of alemtuzumab should be divided over several days, with an initial dose no greater than 3mg to minimize the risk of acute reactions. Subcutaneous administration[21] along with anti-pyretics, anti-histamines, and steroids can help to attenuate patient symptoms. Because of the high incidence of viremias following alemtuzumab, all patients should receive anti-viral prophylaxis, and weekly blood PCR monitoring should be performed. Prophylaxis including anti-Pneumocystis jiroveci and broad anti-fungal therapy (covering filamentous fungi) are warranted.

In conclusion, this series suggests that alemtuzumab therapy of refractory HLH results in improvement and survival to allogeneic HCT in most patients, with an acceptable rate of complications. Future prospective studies to determine optimal dose and timing intervals

and to study the full extent and duration of patient response will further improve the use of this agent.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Figure 2.

Figure 3.

Table I

HLH therapy prior to alemtuzumab.

Patient	Weeks From Initiation of HLH Therapy Until Alemtuzumab	Dexamethasone Received During the 2 Weeks Prior to Alemtuzumab	Etoposide Received During the 2 Weeks Prior to Alemtuzumab	Cyclosporine Received During the 2 Weeks Prior to Alemtuzumab	Intrathecal Therapy Received During the 2 Weeks Prior to Alemtuzumab	Other Therapy Received During the 2 Weeks Prior to Alemtuzumab
1	10	+	+	+	-	-
2	2	+	+	+	-	-
3	10	+	+	-	-	-
4	3	+	+	-	-	-
5	7	+	+	+	-	-
6	14	+	+	-	-	-
7	6	+	+	-	-	-
8	7	+	-	+	+	-
9	14	+	+	-	-	Ara-C
10	7	+	+	-	-	-
11	22	+	-	+	-	-
12	9	+	+	+	+	-
13	4	+	+	+	-	Rituximab
14	3	+	+	-	-	Methylprednisolone
15	11	+	+	-	+	-
16	6	+	+	-	-	-
17	41	+	-	-	+	-
18	36	+	-	-	-	Rituximab
19	15	+	-	-	+	Rituximab
20	6	+	+	-	-	-
21	2	+	+	+	-	-
22	70	+	+	-	-	Methylprednisolone

Features of refractory HLH present prior to alemtuzumab.

Table II

Patient	Splenomegaly and/or Hepatomegaly	Received Blood and/or Platelet Transfusion(s) Within 2 Weeks Pre-		Anemia Within 2 Weeks Pre-Alemtuzumab	Platelet Count (1000/ mL) Day of Alemtuzumab	ANC (cells/ mL) Day of Alemtuzumab	ALT (unit/L) Day of Alemtuzumab	Ferritin (ng/mL)	SolIL2R (unit/mL) (Upper Limit of Normal)	Triglyceride (mg/dL)	Hemophagocytosis Observed on Tissue Biopsy Within 1 Month Prior to Alemtuzumab (Bone Marrow, Lymph Node, Lung, Liver)	Other Pertinent Clinical Information
		Alemtuzumab	Alemtuzumab									
1	+	-		+	158	340	66	3433	9953 (7887)	738	Not Obtained	
2	+	-		+	48	121	1893	47850	NA	376	+	
3	-	+		+	35	420	73	1730	14384 (3026)	NA	Not Obtained	
4	+	+		+	35	70	72	17021	16211 (3026)	429	+	
5	+	+		+	72	637	27	237	5555 (3026)	439	+	
6	+	-		+	350	2010	683	1360	2492 (2126)	227	-	
7	+	+		+	267	9100	200	1431	3409 (4321)	NA	+	Altered Level of Consciousness/ CNS HLH; Tracheostomy and Ventilator Dependent
8	-	+		+	81	0	204	3842	1295 (2126)	391	-	
9	+	+		+	71	0	154	174119	NA	196	-	GI Bleeding, Open Abdomen Following Exploratory Laparotomy; Critically Ill in Intensive Care Unit; Multi-organ Failure
10	-	-		+	16	0	474	1604	4178 (2126)	265	-	
11	-	+		+	97	910	92	4861	3427 (1105)	142	+	
12	+	+		+	105	416	19	991	NA	111	Not Obtained	
13	+	+		+	37	0	33	595	8087 (2678)	170	+	
14	-	-		+	38	0	170	901	990 (1105)	194	+	
15	+	+		+	31	10	129	43848	5367 (1105)	490	Not Obtained	Altered Mental Status; Disseminated Fungal Infection; Critically Ill in

Patient	Splenomegaly and/or Hepatomegaly	Received Blood and/or Platelet Transfusion(s) Within 2 Weeks		Anemia Within 2 Weeks Pre-Alentuzumab	Platelet Count (1000/ mL) Day of Alentuzumab	ANC (cells/ mL) Day of Alentuzumab	ALT (unit/L) Day of Alentuzumab	Ferritin (ng/mL)	SolIL2R (unit/mL) (Upper Limit of Normal)	Triglyceride (mg/dL)	Hemophagocytosis Observed on Tissue Biopsy Within 1 Month Prior to Alentuzumab (Bone Marrow, Lymph Node, Lung, Liver)		Other Pertinent Clinical Information
		Pre-Alentuzumab	Alentuzumab										
16	+	+		+	347 (Recent Transfusion)	1780	57	23828	NA	175	Not Obtained		Intensive Care Unit Critically Ill in Intensive Care Unit
17	–	–		+	301	2700	198	NA	3716 (2678)	477	+		Altered Level of Consciousness/ CNS HLH with Varicella and EBV + CSF; Critically Ill in Intensive Care Unit
18	–	–		+	15	4590	302	8976	1082 (1105)	140	+		
19	+	+		+	47	0	133	23047	3036 (1105)	NA	+		
20	+	+		+	37	30	40	9021	15892 (2678)	325	–		Critically Ill in Intensive Care Unit
21	Not Known	+		+	13	0	77	>20,000	2857 (1105)	562	+		
22	+	+		+	30	6400	757	46165	14680 (1105)	255	+		

NA, not available; CNS, central nervous system; CSF, cerebrospinal fluid

Alentuzumab and responses.

Table III

Patient	Total First or Only Course Alentuzumab Dose (mg/kg)	Days Over Which Alentuzumab Course was Divided	ANC (cells/mL)		ALT (unit/L)		Ferritin (ng/mL)		SoiHL2R [unit/mL] (Upper Limit of Normal)		Triglyceride (mg/dL)		Hemophagocytosis Observed on Tissue Biopsy Within 1 Month Prior or 1 Month Following Alentuzumab (Bone Marrow, Lymph Node, Lung, Liver)		Clinically Symptomatic CNS HLH/ Altered Level of Consciousness		Overall Partial Response
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
1	8.9 ^a	4	340	860 ^b	66	79	3433	1242	9953 (7887)	2879 (7887)	738	286	NA	–			+
2	6.1	4	121	3590	1893	794	47850	3294	NA	1640 (7887)	376	351	+	NA			+
3	0.2	3	420	1560	73	103	1730	NA	14384 (3026)	NA	NA	NA	NA	NA			+/-
4	1.1 ^a	6	70	820	72	152	17021	13120	16211 (3026)	4031 (3026)	429	344	+	+			+
5	1.0	5	637	19039	27	NA	237	722	5555 (3026)	5237 (3026)	439	474	+	+			+/-
6	0.5 ^a	3	2010	2620	683	132	1360	944	2492 (2126)	1454 (2126)	227	146	–	+			+
7	3.4 ^a	8	9100	6140	200	140	1431	987	3409 (4321)	2583 (4321)	NA	NA	+	+	+	+	+/-
8	0.6 ^a	4	0	2180	204	156	3842	4374	1295 (2126)	2735 (2126)	391	110	–	–			+
9	1.0	4	0	0	154	31	174119	12111	NA	NA	196	NA	–	–			+/-
10	1.1	4	0	0	474	54	1604	1471	4178 (2126)	1493 (2126)	265	140	–	–			+
11	0.4	2	910	960	92	61	4861	6799	3427 (1105)	3564 (1105)	142	198	+	NA			–
12	1.0 ^a	6	416	240	19	219	991	4716	NA	NA	111	205	NA	NA			–
13	0.4 ^a	5	0	15750	33	31	595	1401	8087 (2678)	2256 (2678)	170	230	+	+			+
14	1.0	4	0	2410	170	68	901	1625	990 (1105)	820 (1105)	194	78	+	–			+
15	1.0	4	10	1680	129	489	43848	5319	5367 (1105)	NA	490	183	NA	NA			+
16	0.9	4	1780	14880	57	23	23828	3796	NA	NA	175	129	NA	NA			+
17	2.4	10	2700	100	198	96	NA	NA	3716 (2678)	NA	477	340	+	–			+
18	0.5 ^a	4	4590	3100	302	439	8976	12087	1082 (1105)	337 (1105)	140	170	+	NA			–
19	0.7 ^a	4	0	3670	133	71	23047	NA	3036 (1105)	NA	NA	NA	+	NA	+	+	+/-
20	0.7 ^a	4	30	13550	40	69	9021	5010	15892 (2678)	2537 (1105)	325	NA	–	NA			+
21	0.1 ^a	2	0	19000	77	45	>20,000	10956	2857 (1105)	NA	562	233	+	–			+
22	0.8	4	6400	2000	757	222	46165	19030	14680 (1105)	6963 (1105)	255	NA	+	NA			+

CNS, central nervous system; HLH hemophagocytic lymphohistiocytosis; NA, not available

^a Later received 1 or more additional courses;
^b Values in bold type represent a response