MAJOR ARTICLE

Infectious Complications Associated with Alemtuzumab Use for Lymphoproliferative Disorders

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Background. Alemtuzumab is an emerging therapy for refractory lymphoproliferative disorders. The associated long-term risks of infection remain poorly defined.

Methods. From July 2001 through December 2003, all patients who received alemtuzumab for the treatment of lymphoproliferative disorders at 1 institution underwent a retrospective evaluation to document infectious complications until death or end of follow-up in October 2004. Alemtuzumab recipients who underwent allogeneic hematopoietic stem cell transplantation were compared with a concurrent cohort who also underwent allogeneic hematopoietic stem cell transplantation but did not receive alemtuzumab.

Results. Twenty-seven patients were identified (21 with chronic lymphocytic leukemia and 6 with plasma cell disorders). The overall mortality was 37%, with 7 of 10 deaths being related to infection. Significant opportunistic infections occurred in 9 patients (43%) with chronic lymphocytic leukemia, including cytomegalovirus, progressive multifocal leukoencephalopathy, adenovirus, toxoplasmosis, and acanthamaebiasis. Thirty nonopportunistic infections in 22 patients (82%) were also identified. The 3 deaths related to nonopportunistic infections all involved *Enterococcus* species bacteremia. When compared with a concurrent chronic lymphocytic leukemia cohort that underwent allogeneic hematopoietic stem cell transplantation, alemtuzumab recipients had an incidence of cytomegalovirus reactivation of 66.7% (6 of 9 patients), compared with 37% in the non-alemtuzumab group (10 of 27 patients; $P = .15$), and an incidence of post-transplant opportunistic infections (excluding herpesviruses) of 44.4% (compared with 29.6% in the non-alemtuzumab group; $P = .41$).

Conclusions. Despite the use of herpesvirus and *Pneumocystis* pneumonia prophylaxis, serious infectious complications occur in patients receiving alemtuzumab for lymphoproliferative disorders. Infectious complications are more varied and diverse in patients receiving alemtuzumab than has been reported in trials to date.

Immunotherapy is increasingly being used for the treatment of refractory malignancies. Monoclonal antibody therapy offers a unique mechanism of action that can selectively eradicate its targets and may have less toxicity than traditional chemotherapy and radiotherapy.

Alemtuzumab (Campath-1H; Genzyme) is a humanized monoclonal IgG1 antibody directed toward the cell surface antigen CD52. When administered, the binding of this antibody-antigen complex leads to the lysis of lymphocytes and other cells expressing CD52 through complement activation and antibody-dependent cell-mediated toxicity [1]. Clinical trials indicate that alemtuzumab has efficacy in the treatment of malignancies, such as non-Hodgkin lymphoma, B cell chronic lymphocytic leukemia (CLL), and T cell prolymphocytic leukemia [2–4]. It has also been used in other diseases mediated by the immune system, such as acute rejection of solid-organ transplants [5], rheumatoid arthritis [6], and graft-versus-host disease [7]. Because of its ability to deplete T cell populations, alemtuzumab has also been used as a conditioning agent in solid-organ transplantation and hematopoietic stem cell transplantation (HSCT) [8–10].

Alemtuzumab use may increase risk of infection. Lymphocyte depletion has lead to significant infection-related complications, as reported in all trials to date.

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This is likely to be related to loss of circulating T cells, which results in defective cell-mediated immunity in patients who already have dysfunctional immune systems because of previous or concurrent therapy with traditional chemotherapy, radiation, or other immunotherapies. These patients can experience, as well, the cumulative effects of bone marrow depression from their underlying malignancies or HSCT, increasing their net state of immunosuppression and subsequent risk for opportunistic infections (OIs) [11].

This study identifies the infectious complications seen in this patient population by evaluating the alemtuzumab experience of patients being treated for lymphoproliferative disorders in a single institution over a 2.5-year period. Comparisons are made among patients who have undergone allogeneic HSCT and with the data from published trials.

METHODS

All patients who initiated treatment with alemtuzumab at Dana Farber Cancer Institute/Brigham & Women's Hospital (DFCI/BWH Partners Cancer Care [Boston, MA]) from 1 July 2001 to 31 December 2003 were identified by review of the pharmacy database and by a systematic search of electronic medical records in the Partners Healthcare's Research Patient Data Repository, which can identify patients with specific demographic characteristics, diagnoses, laboratory test results, medications, molecular medicines, health histories, microbiological test results, procedures, providers, and/or transfusion services. Detailed review of paper and electronic medical records of the identified cohort was performed. Information was collected, including age, sex, the condition being treated with alemtuzumab, date of original diagnosis, all previous treatment regimens, time from diagnosis of underlying condition to alemtuzumab treatment, and accumulated alemtuzumab treatment at the time of censoring events. All incident infections occurring from initiation of alemtuzumab until death or end of follow-up on 31 October 2004 were documented.

Infections were classified as OIs on the basis of the infecting organism and syndrome [12]. Specifically, OIs include invasive fungal infections (classified in accordance with the consensus of the Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer and Mycoses Study Group of the National Institute of Allergy and Infectious Disease [13]); progressive multifocal leukoencephalopathy (PML); localized reactivation of herpesviruses; disseminated viral infections caused by herpesviruses and others, such as adenovirus, causing end-organ disease; invasive pyomyositis; and parasitic infections, such as cerebral toxoplasmosis and disseminated achanthamebiasis. Nonopportunistic infections (NOIs) include bacterial pneumonia, bacteremia (catheter-related or related to other organ involvement at normally nonsterile sites [e.g., gastrointestinal tract]), cellulitis, *Clostridium difficile*–associated colitis, and respiratory viral infections without dissemination. Date of diagnosis, mode of diagnosis, treatment, and outcome of each infection was recorded. Diagnosis of each infection was based on the standard methods, including microbial cultures of normally sterile sites, pathological criteria from biopsy specimens, and molecular markers of active disease.

Several alemtuzumab recipients subsequently underwent allogeneic HSCT for treatment of CLL. A concurrent cohort of all CLL patients who underwent allogeneic HSCT during the same period was compiled for comparison of survival rates and OI risk. Additional information related to HSCT that was collected included date of HSCT, conditioning regimens, HLA matching with donor, cytomegalovirus (CMV) serostatus of the donor and recipient, and whether acute or chronic graft-versus-host disease occurred. The study was approved by the Office for the Protection of Research Subjects of Dana-Farber/Harvard Cancer Center.

A two-sided Fisher's exact test or Wilcoxon test were used as appropriate for analysis of baseline characteristics and other 2-group comparisons. Kaplan-Meier curves were calculated to assess overall survival, time to CMV and non-CMV OIs in the alemtuzumab recipient groups and among CLL patients who had undergone HSCT (data not shown). Log-rank tests were performed to assess for statistical significance.

Reports of infectious complications of alemtuzumab use in the literature were restricted to published trials in the treatment of lymphoproliferative disorders, such as CLL and non-Hodgkin lymphoma. Abstracts, individual case reports, and non-English published reports were excluded. Reports were identified using the search terms "alemtuzumab" and "Campath."

RESULTS

A total of 27 patients were identified as having received alemtuzumab from July 2001 through December 2003. There was no loss to follow-up. Alemtuzumab was administered intravenously, except in 1 instance in which subcutaneous injections alone were used. Regimens consisted of escalating doses that started at 3 mg and then increased to 10 mg before escalating to 30 mg given up to 3 times per week. One patient could not tolerate 30 mg as a maximum dose and was treated with 20 mg instead. Treatment regimens ranged from a minimum of 4 doses in 1 patient to a maximum of 44 doses in 2 patients.

Characteristics of alemtuzumab recipients. Of the 27 patients identified, 21 had a diagnosis of CLL, 5 had Waldenstrom macroglobulinemia, and 1 had an IgG-secreting lymphoplasmocytic lymphoma (table 1). Nineteen patients were male and 8 were female, consistent with the predilection of CLL toward the male sex [14]. The median age at initiation of alemtuzumab was 56 years (range, 40–66 years). The median cumulative dose of alemtuzumab among all 27 patients was 413 mg (range, 53–

Table 1. Baseline characteristics of patients receiving alemtuzumab.

Characteristic	All patients (n = 27)	Patients with chronic lymphocytic leukemia (n = 21)	Patients with plasma cell disorder (n = 6)	P[a]
Male sex	19 (70.4)	16 (76.2)	3 (50)	
Age at diagnosis, median years (range)	49 (34–64)	47 (34–64)	50 (42–55)	
Age during alemtuzumab treatment, median years (range)	56 (41–67)	56 (41–67)	57 (43–62)	
Time to alemtuzumab therapy after diagnosis, median years (range)	6 (0–13)	5.5 (0–13)	8 (1–13)	
Chemotherapeutic regimens prior to alemtuzumab therapy, median no. (range)	4 (1–13)	3 (1–13)	4.5 (3–5)	
Pre-alemtuzumab chemotherapy				
Fludarabine	23 (85.2)	21 (100)	2 (33.3)	.0009
Rituximab	19 (70.4)	13 (61.9)	6 (100)	
Cyclophosphamide	19 (70.4)	15 (71.4)	4 (66.7)	
Corticosteroids	18 (66.7)	13 (61.9)	5 (83.3)	
Vincristine	15 (55.6)	11 (52.4)	4 (66.7)	
Chlorambucil	9 (33.3)	7 (33.3)	2 (33.3)	
Doxorubicin	9 (33.3)	6 (28.6)	3 (50)	
Thalidomide	4 (14.8)	1 (4.8)	3 (50)	.02
Cladribine	3 (11.1)	0 (0)	3 (50)	.007
Cytarabine	2 (7.4)	2 (9.5)	0 (0)	
Methotrexate	1 (3.7)	1 (4.8)	0 (0)	
Cisplatin	1 (3.7)	1 (4.8)	0 (0)	
Etoposide	1 (3.7)	1 (4.8)	0 (0)	
Bleomycin	1 (3.7)	1 (4.8)	0 (0)	
Mitoxantone	1 (3.7)	1 (4.8)	0 (0)	
IL-2	1 (3.7)	0 (0)	1 (16.7)	
IFN-α	1 (3.7)	0 (0)	1 (16.7)	

NOTE. Data are no. (%) of patients, unless otherwise indicated.

[a] Only statistically significant P values are presented.

1179 mg). The median cumulative dose for the patients with CLL was 413 mg (range, 53–1179 mg), and for patients with plasma cell disorders, it was 614.5 mg (range, 343–1033 mg). These differences were not statistically significant. The median follow-up time after starting alemtuzumab was 369 days (range, 22–1164 days) with 10 patients (37%) dying during this time. Seven of the 10 deaths could be attributed to infection (4 OIs and 3 NOIs). All patients received trimethoprim-sulfamethoxazole, atovaquone, or inhaled pentamidine for *Pneumocystis jiroveci* (PCP) prophylaxis and received either acyclovir or famciclovir for herpesvirus prophylaxis. CMV surveillance with a hybrid-capture assay (Digene Corporation) was performed systematically during each follow-up outpatient visit and during every hospitalization.

OIs. Of the 27 patients, 15 (56%) developed an OI during the study period. Herpesvirus infections were the most common, with CMV viremia occurring in 44% of patients (11 patients with CLL and 1 patient with plasma cell disorder). End-organ disease with evidence of colitis and pneumonitis was seen in 1 patient who died from this complication. Evidence of dissemination with other herpesviruses was not identified.

Significant morbidity from OIs occurred in the CLL group alone (table 2). Excluding the patients with CMV viremia without evidence of end-organ disease and patients with localized herpes simplex virus and varicella-zoster virus infections, there were 12 OIs identified in 9 (43%) of 21 patients as follows: 3 cases of invasive pulmonary aspergillosis, 2 cases of pyomyositis and bacteremia, and 1 case each of adenoviral pneumonia, PML, disseminated histoplasmosis, disseminated cryptococcosis, cerebral toxoplasmosis, disseminated acanthamoebiasis, and CMV pneumonitis and colitis. Four of the 12 episodes were diagnosed during periods of neutropenia (absolute neutrophil count, $\leqslant$500 cells/mL). Three of those 4 cases were noted to occur in patients who were neutropenic within the 30 days prior to the diagnosis. Of the 9 patients with significant OIs, 4 died because of infection-related reasons, 1 of whom had undergone an allogeneic HSCT. The cumulative alemtuzumab dose administered among the CLL group did not significantly differ between those who had OIs and those who did not. Among the 9 patients who developed significant OIs, the median dose at the time of diagnosis was 379 mg (range, 53–1129 mg), which was not significantly different from the me-

Table 2. Opportunistic infectious complications after alemtuzumab treatment.

Infection	No. of patients	No. of HSCTs	Cumulative dose, median mg (range)[a]	Time to clinical infection, median days (range)[b]	No. of deaths[c]
Viral					
Adenovirus pneumonia	1	0	253	274[d]	1
CMV viremia	12	4	253 (3–942)	175 (0–652)	1
CMV pneumonitis and colitis	1	0	103	351	1
HSV infection (localized)	2	1	200 (56–343)	62 (52–72)	0
PML	1	0	379	100	1
VZV infection (localized)	1	0	973	540	0
Bacterial					
Group B *Streptococcus* pyomyositis/bacteremia	1	1	73	8	0
Staphylococcus aureus pyomyositis/bacteremia	1	1	53	570	0
Fungal					
Pulmonary aspergillosis	3	2	56 (53–1129)	120 (79–662)	0
Disseminated cryptococcosis	1	0	379	171	0
Disseminated histoplasmosis	1	1	596	298	0
Parasitic					
Cerebral toxoplasmosis	1	1	553	169	0
Disseminated achanthamebiasis	1	1	942	443	1

NOTE. CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; HSCT, hematopoietic stem cell transplantation; HSV, herpes simplex virus; PML, progressive multifocal leukoencephalopathy; VZV, varicella-zoster virus.

[a] Total amount of alemtuxzumab received at the time of diagnosis of the infection.
[b] No. of days after receiving first dose of alemtuzumab that the infection was diagnosed.
[c] Death attributed to the specified infection.
[d] Estimated date based on known records.

dian dose among those who did not develop OIs, which was 446 mg (range, 103–1179 mg). The median time to development of an OI after starting alemtuzumab treatment was 169 days (8–570 days). Other potential differences, such as sex, age, cumulative chemotherapy prior to alemtuzumab therapy, and time from diagnosis of malignancy to the initiation of alemtuzumab therapy did not differ significantly between those who developed an OI and those who did not (data not shown).

NOIs. NOIs were more common than OIs, with 30 NOIs among 22 (82%) of the 27 patients (table 3). Upper respiratory tract infections were most commonly diagnosed, followed by sepsis and/or bacteremia and catheter-related infections. Among the 8 episodes of sepsis and/or bacteremia, *Enterococcus* species were the most common etiological agent (3 cases). Two of the 3 cases were attributable to vancomycin-resistant *Enterococcus*, and mortality was 100% among all 3 cases. One of the patients with vancomycin-resistant *Enterococcus* bacteremia at the time of death also had an intraabdominal abscess.

Table 3. Nonopportunistic infectious complications after alemtuzumab treatment.

Infection	No. of patients	Cumulative dose, median mg (range)[a]	Time to infection, median days (range)[b]	No. (%) of deaths[c]
Viral				
Upper respiratory tract	22	626 (56–1179)	465 (37–899)	0 (0)
Lower respiratory tract	3	79.5 (53–106)	129 (102–815)	0 (0)
Bacterial				
Catheter-related	8	553 (103–1033)	169 (16–353)	0 (0)
Bacteremia/septicemia	8	343 (56–949)	232 (17–411)	3 (37.5)
Pneumonia	6	553 (53–856)	358 (95–575)	0 (0)
Cellulitis	4	531 (227–973)	264 (28–593)	0 (0)
Clostridium difficile–associated colitis	1	103	187	0 (0)
Polymicrobial intraabdominal abscess[d]	1	106	389	1 (100)

[a] Median dose of alemtuzumab received at the time of infection diagnosis.
[b] Median no. of days to diagnosis of infection after receiving the first dose of alemtuzumab.
[c] Death attributed to the specified infection.
[d] This patient also had vancomycin-resistant *Enterococcus* bacteremia at the time of his death.

Table 4. Characteristics of patients with allogeneic hematopoietic stem cell transplantation with chronic lymphocytic leukemia, stratified by treatment with alemtuzumab.

Characteristic	Alemtuzumab group (n = 9)	Non-alemtuzumab group (n = 27)
Age, median years (range)	56 (42–65)	45 (27–63)
Male sex	88.9	81.5
HLA matching		
Matched-unrelated	77.8	63
Matched-related	11.1	25.9
Mismatched-related	11.1	0
Mismatched-unrelated	0	11.1
Conditioning regimen		
Cyclophosphamide	22.2	14.8
Total body irradiation	33.3	14.8
Busulfan	66.7	85.2
Fludarabine	66.7	85.2
Antithymocyte globulin	11.1	0
CMV D/R serostatus[a]		
D−/R−	42.9	29.6
D−/R+	0	22.2
D+/R−	28.6	29.6
D+/R+	28.6	18.5
Acute GVHD[b]	66.7	44
Chronic GVHD	55.6	55.6
Follow-up, median days (range)[c]	757 (149–1084)	456 (27–825)
Mortality	44.4	44.4

NOTE. Data are % of patients, unless otherwise indicated. CMV, cytomegalovirus; D/R, donor and recipient; GVHD, graft-versus-host disease.

[a] CMV donor serostatus was not known in 2 of the 7 patients receiving alemtuzumab.

[b] GVHD was not known in 2 of the 25 patients not receiving alemtuzumab.

[c] Days after undergoing hematopoietic stem cell transplantation.

Analysis of CLL allogeneic HSCT recipient cohort according to alemtuzumab use. Among the 27 patients who received alemtuzumab, 9 underwent allogeneic HSCT for further treatment of CLL. These patients were compared with the remaining patients in the DFCI/BWH CLL cohort who underwent allogeneic HSCT during the same time period but who did not receive alemtuzumab (27 patients). In the alemtuzumab group, follow-up extended to a median 757 days, compared with the median follow-up time in the non-alemtuzumab group, which was 456 days. Their baseline characteristics were otherwise similar (table 4). Infectious complications between the 2 groups are outlined in table 5. Those who received alemtuzumab had an incidence of CMV viremia of 66.7% (CMV viremia incidence in the non-alemtuzumab group, 37%; $P = .15$) and an incidence of post-transplant OI (excluding herpesviruses) of 44.4% (post-transplant OI incidence in the non-alemtuzumab group, 29.6%; $P = .41$). Invasive pulmonary aspergillosis was the most common OI. There were 2 cases of PCP among the non-alemtuzumab group and none among the alemtuzumab group. Prophylaxis administration and adherence was 100% among the alemtuzumab group, but nonadherence was a factor in both cases of PCP in the non-alemtuzumab group.

Survival rates after HSCT among the alemtuzumab and non-alemtuzumab recipients were similar. The 25th percentile survival rate among the non-alemtuzumab recipients was 196 days (95% CI, 111–341 days), and it was 345 days among alemtuzumab recipients (95% CI, 149–1084 days; $P = .65$ by log-rank test).

Literature review. Table 6 outlines the infectious complications recorded in the published trials regarding alemtuzumab use in the treatment of lymphoproliferative disorders. Fever of unknown origin and mucositis as infectious complications were excluded. Results from these past reports are varied, though all reports have noted at least some infectious complications. Two of the trials were prematurely closed after internal review because of infectious complications [16, 23]. Among the cumulative total of patients in these studies ($n = 410$), there were 262 episodes of infection, 167 (63.7%) of which were OIs. This excludes 3 cases of Epstein-Barr virus–related large cell lymphoma that developed in patients with underlying CLL noted in only 1 of the trials [22]. Analysis by specific type of OI shows that herpes simplex virus reactivation was the most common OI (54 [32.3%] of 167 cases), followed closely by CMV reactivation (52 [31.1%] of 167 cases), which included 8 cases of pneumonitis and 1 case of colitis [2, 14–16, 21, 23]. Other herpesvirus infections noted include varicella-zoster virus (7 [4.2%] of 167 cases) and 1 case of human herpesvirus-6 reactivation. Following the herpesviruses, the most common OI included PCP (11 [6.6%] of 167 cases) and invasive pulmonary aspergillosis (10 [6%] of 167 cases). Other notable OIs include 2 cases of tuberculosis, 2 cases of cutaneous nontuberculous mycobacterial infections, 2 cases of sinosal zygomycosis, 1 case of pulmonary cryptococcosis, and 1 case of PML.

Among the 95 NOIs, sepsis was the most commonly diagnosed problem (28 [29.5%] of 95 cases). Bacteremia with no specific link to sepsis was identified as well (15 [15.8%] of 95 cases). The most common organism identified was *Escherichia coli*. Pneumonia was almost equally as common as sepsis (27 [28.4%] of 95 cases). Less common were 10 cases (10.5%) of other nonspecific respiratory tract infections (sinusitis and bronchitis), 2 episodes of urinary tract infections, 3 cases of infection with *Listeria monocytogenes* (1 linked to meningitis alone, 1 to both bacteremia and meningitis, and 1 unspecified), 1 case of presumed viral myocarditis, and 1 case of presumed infectious gastroenteritis. The overall infection-related mortality for both OIs and NOIs was 7.1% (29 of 410 patients).

Table 5. Incident infections among patients with chronic lymphocytic leukemia after allogeneic hematopoietic stem cell transplantation (HSCT), stratified by treatment with alemtuzumab.

Infection	Alemtuzumab group (n = 9)		Non-alemtuzumab group (n = 27)	
	No. of patients	Time after HSCT, median days (range)[a]	No. of patients	Time after HSCT, median days (range)[a]
Viral				
RSV[b]	2	347.5 (35–660)	0	0
BK virus cystitis	0	0	2	62 (30–94)
CMV viremia	6	208 (27–497)	10	284 (22–378)
Bacterial				
Bacteremia	5	246 (141–354)	9	129 (11–213)
Catheter-related	5	239 (77–904)	9	83 (14–757)
Pneumonia	4	298 (100–888)	5	189 (124–341)
Clostridium difficile–associated colitis	1	9	1	119
Cellulitis	2	361 (232–489)	1	82
Intraabdominal abscess	1	322	0	0
Sinusitis	0	0	1	729
Lyme disease	0	0	1	716
UTI	0	0	2	93 (43–143)
Fungal and parasitic				
IPA	2	469 (431–507)	2	165 (116–213)
Aspergillus species endopthalmitis	0	0	1	24
Cunninghamella species pneumonia/encephalitis	0	0	1	400
Disseminated histoplasmosis	1	431	0	0
Toxoplasmosis gondii encephalitis	1	699	0	0
Disseminated acanthamoebiasis	1	263	0	0
Pneumocystis jiroveci pneumonia	0	0	2	100 (90–110)

NOTE. CMV, cytomegalovirus; IPA, invasive pulmonary aspergillosis; RSV, respiratory syncytial virus; UTI, urinary tract infection.

[a] Median no. of days after HSCT that infection was diagnosed.

[b] No evidence of pneumonia.

DISCUSSION

Alemtuzumab was approved by the US Food and Drug Administration in 2001 for the treatment of refractory CLL [24]. The spectrum and timing of infectious complications that may be predicted from prolonged lymphocyte depletion has not been well defined to date. The depletion of lymphocytes induced by alemtuzumab can be profound within the first month of therapy, and the reconstitution of the lymphoid cell line can be delayed for up to 2 years [25] (median delay, 9 months) [26]. In CLL, clonal lymphocytosis makes it difficult to relate the degree of lymphopenia with risk of infection on routine testing. Patients receiving alemtuzumab in clinical practice thus far are typically pretreated with multiple regimens of other chemotherapeutic agents, adding to an already-increased risk for significant infection.

The data from the 27 alemtuzumab recipients in this series show a wide variety of infectious complications. Herpesvirus infection was the most frequently encountered infectious complication, but with acyclovir prophylaxis and systematic monitoring of CMV viremia, serious complications were infrequent. Only 1 patient experienced end-organ disease and death associated with CMV. Other notable viral infections included adenoviral pneumonia and 1 case of PML, both of which contributed to patient mortality. PML had been noted before in only 1 earlier study of alemtuzumab [18]. Other OIs of concern included infection with invasive noncandidal fungi, such as histoplasmosis, cryptococcosis, and aspergillosis. Significant parasitic infection, such as cerebral toxoplasmosis and acanthamoebiasis, were also noted. This represents a wide variety of serious OIs in a relatively small number of patients. In particular, PML and cerebral toxoplasmosis are rarely otherwise reported in CLL patients.

The majority of the patients had CLL as their underlying malignancy, which is associated by itself with increased frequency of infection. It is interesting to note that, in the group of patients with plasma cell disorders, aside from cutaneous herpesvirus infections and CMV viremia, no OI complications were observed during the follow-up period. The number of

Table 6. Infectious complications of alemtuzumab in lymphoproliferative disorders reported in the literature.

Study	No. of patients	Opportunistic infections reported (no. of cases)	Nonopportunistic infections reported (no. of cases)	No. (%) of deaths related to infection
[15]	9	CMV pneumonitis (1); oral candidiasis (1)	…	0 (0)
[16]	7	HSV reactivation (5); CMV colitis (1); CMV viremia (2); PCP (1)	*Listeria monocytogenes* bacteremia with meningitis (1); α-hemolytic streptococcal bacteremia (1); UTI (1)	0 (0)
[17]	29	HSV reactivation (11); oral candidiasis (5); PCP (2)	Pneumonia *(Streptococcus pneumoniae, Haemophilus influenzae,* and unidentified organisms) (4); septicemia *(Klebsiella pneumoniae, Staphylococcus aureus,* and unidentified organisms) (4)	0 (0)
[2]	50	HSV reactivation (22); oral candidiasis (13); CMV pneumonitis (3); IPA (2); disseminated tuberculosis (1); PCP (1)	Pneumonia (unidentified organism) (7); septicemia *(Escherichia coli, Staphylococcus* species, and unidentified organisms) (9)	4 (8)
[18]	18	HSV reactivation (7); oral candidiasis (1); PML (1)	*S. aureus* pneumonia (3); bacteremia *(E. coli, S.* Typhimurium) (2); other respiratory tract infections (4); UTI (1)	3 (16.7)
[19]	9	CMV reactivation (3)	…	0 (0)
[4]	93	CMV reactivation (7); HSV reactivation (6); PCP (1); IPA (3); *Cryptococcus neoformans* pneumonia (1); rhinocerebral mucormycosis (1); candidemia (1); VZV infection (4)	*L. monocytogenes* meningitis (1); septicemia (unidentified gram-positive organisms, *E. coli,* and *Pseudomonas aeruginosa)* (14); candidiasis (9)	15 (16.1)
[20]	41	CMV reactivation (4); PCP (1)	…	0 (0)
[21]	24	PCP (4); IPA (2); disseminated VZV infection (1); nonspecific mycobacterial pneumonia (1); CMV pneumonitis (1); *Candida* infection[a] (2)	Pneumonia *(Legionella* species and *Klebsiella* species) (2)	2 (8.3)
[3]	78	CMV reactivation (15); HSV reactivation (2); disseminated VZV (1); PCP (1); IPA (2); nontuberculous *Mycobacterium* skin infections (2); sinosal zygomycosis (1)	Pneumonia *(S. aureus* and unidentified organisms) (9); peritonitis with *S. aureus* bacteremia (1); bacteremia *(E. coli, S. aureus, Strenotrophomonas maltophilia, Staphylococcus, Enterococcus, Acinetobacter, Corynebacterium, Stomatococcus,* and *Micrococcus* species, and other unidentified gram-positive cocci) (11); other respiratory tract infections (3)	4 (5.1)
[22]	41	CMV reactivation (8); CMV pneumonitis (1)	Viral myocarditis (1); listeriosis (1); pneumonia (unidentified organism, influenza A) (2); septicemia (unidentified organism) (1); other upper respiratory tract infections (1)	1 (2.4)
[23]	11	IPA (1); CMV reactivation (4); CMV pneumonitis (2); HSV reactivation (1); HHV-6 reactivation (1); VZV reactivation (1); pulmonary tuberculosis (1)	Other respiratory tract infections (2); gastroenteritis (1)	0 (0)

NOTE. CMV, cytomegalovirus; HHV-6, human herpesvirus 6; HSV, herpes simplex virus; IPA, invasive pulmonary aspergillosis; PCP, *Pneumocystis jiroveci* pneumonia; PML, progressive multifocal leukoencephalopathy; UTI, urinary tract infection; VZV, varicella-zoster virus.

[a] This report did not specify the type of *Candida* infection.

patients was small in this subgroup (6 patients), but this could reflect differences in the underlying pathology and treatment of the malignancy.

To further elucidate risk of infection attributable to alemtuzumab for those with CLL and to minimize the probability of confounding by indication, we compared patients with CLL treated with alemtuzumab who underwent allogeneic HSCT with a concurrent cohort of patients with CLL who underwent allogeneic HSCT but did not receive alemtuzumab. We found that OIs were more frequent among patients who received alemtuzumab, but not in a statistically significant manner. This may be because of a relatively small sample size. Survival rates were also similar between the 2 groups. This could be because of timely identification and effective treatment of some of the OIs observed.

Compared to the published reports from earlier trials in table 6, the DFCI/BWH experience with alemtuzumab shows a higher proportion of OIs (27 total OIs, including herpesvirus infection, among the group of 27 patients who received alemtuzumab versus 167 OIs among 410 patients from previous trials). This may be because of the extended follow-up period in this report. The differences in herpes simplex virus and PCP between the DFCI/BWH cohort and the cohorts of previously published trials can be attributed to active use of prophylaxis, which is now a standard recommendation [27]. All patients in the alemtuzumab group from DFCI/BWH were consistently given prophylaxis for both of these infections. Excluding these exceptions, the finding of CMV reactivation and invasive pulmonary aspergillosis as the 2 most commonly seen OIs are consistent with previous studies.

The proportion of NOIs was also higher (30 NOIs among the 27 DFCI/BWH patients receiving alemtuzumab versus 95 NOIs among the 410 patients from previous trials). Among the NOIs, nonspecific upper respiratory tract infections were frequent in our cohort, though no serious mortality-related events were noted. Some published studies made no mention of these diagnoses. The more serious infections (i.e., sepsis and/or bacteremia) were more common, especially if catheter-related infections are included (16 infections among the 27 DFCI/BWH patients receiving alemtuzumab versus 43 infections among the 410 patients in the literature review). Pneumonia was the second most frequent infection.

The treatment of chronic lymphoproliferative disorders has been advanced though the use of monoclonal antibody therapy, such as alemtuzumab. Increased risk and severity of infection have been identified. The overall clinical success of alemtuzumab-treated patients calls for an appropriate therapeutic prescription [28] to manage this excess risk of infection. The risk attributable to alemtuzumab has been difficult to measure because of confounding factors in patient care, such as use of other immunosuppressants, severity and nature of the underlying malignancy, geographic location of the patient, subsequent environmental exposures, and variability in oncologic treatment plans that have to be tailored to the individual patient. With significant lymphopenia lasting up to 2 years [25], following up with patients over an extended period is necessary to appropriately address this excess risk.

This study is the first attempt to quantify this risk in all patients receiving alemtuzumab at a single institution. Although the study is limited by the nature of the study and the relatively small sample size, it can be inferred that the overall risk of OI is higher among this patient population, compared with populations described in previously published data. An understanding of the spectrum and timing of OI after alemtuzumab treatment is central to the successful clinical management of infectious risks and overall success of the therapeutic strategy. Acyclovir use and PCP prophylaxis are warranted among this patient population and appear to provide a benefit. The variety of infections observed makes it difficult to recommend additional universal prophylaxis strategies, such as routine use of antifungal agents. Heightened suspicion on the part of the clinician for investigating and making a specific diagnosis of possible infections and careful weighing of the risks and benefits of alemtuzumab use are required.

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