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ORIGINAL ARTICLE

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Abstract Infection is a significant cause of morbidity and death in patients with chronic lymphocytic leukemia (CLL). Increased infectious events may arise from the multiple courses of immunosuppressive therapy and progressive deterioration of a patient's immune system over the course of disease. The humanized, anti-CD52 monoclonal antibody alemtuzumab (Campath or Campath-1H) has shown notable activity for both untreated and fludarabine-refractory CLL. The antibody not only targets malignant cells but also affects normal, healthy immune cells. The cumulative effects of the malignancy and successive courses of treatments adversely impinge on a patient's defense response to certain bacterial, fungal, and viral infections. In this review article, we provide an overview of common infectious events associated with alemtuzumab therapy in CLL. We also discuss recommendations for effectively monitoring and managing infections in CLL patients.

Keywords Alemtuzumab · Campath · CLL · Infection · Management

T. Elter (✉) · J. J. Vehreschild · O. A. Cornely · A. Engert · M. Hallek
Department of Hematology, Oncology and Infectious Diseases, University of Cologne,
Joseph-Stelzmann-Str.9,
50823 Cologne, Germany
e-mail: thomas.elter@uk-koeln.de

J. Gribben
Cancer Research UK, Barts and the London School of Medicine, London, UK

O. A. Cornely
Center for Clinical Trials, University of Cologne, Cologne, Germany

Background

As one of the most common types of leukemia, B-cell chronic lymphocytic leukemia (CLL) afflicts approximately <1 to 5.5 per 100,000 people and accounts for 22% to 30% of leukemia cases worldwide [28, 51]. Although the disease remains incurable without allogeneic transplantation at present, the development of a number of chemotherapeutic (alkylating agents, nucleoside analogues, and novel drugs) and targeted immunotherapeutic agents (monoclonal antibodies) has improved clinical outcomes in patients with CLL [39, 52, 62].

Alemtuzumab is a humanized monoclonal antibody that binds to the CD52 antigen, which is present on an array of mature hematopoietic cells, including lymphocytes, monocytes, macrophages, and eosinophils, but not on progenitor cells [17]. Its mechanism of action includes complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity, and probably apoptosis [41, 50, 55, 63]. Single-agent alemtuzumab is highly effective as both first-line treatment for CLL and treatment for relapsed/fludarabine-refractory CLL, and has been approved for both indications [24, 30]. Alemtuzumab is also being evaluated intensively in the settings of combination therapy [12], consolidation therapy [14, 32, 37, 43, 61], and as part of the conditioning regimen for patients undergoing autologous [37] or allogeneic stem cell transplantation (SCT) [10].

Despite its remarkable efficacy, alemtuzumab therapy can frequently be accompanied by serious, sometimes even life-threatening complications, including cytopenia and subsequent infections. Careful monitoring and management of infectious events will be required in order to fully harness the benefit of alemtuzumab therapy and improve the clinical outcome in CLL patients. The overview and management recommendations provided in this article aim to help

physicians better understand and manage alemtuzumab-associated infections in routine clinical practice setting.

Patient predisposition to infections

Patients with CLL may have immune dysfunctions inherent to the disease process that predispose them to infections. Microarray analysis revealed differential gene expression patterns in $CD4^+$ and $CD8^+$ T cells isolated from CLL patients and age-matched healthy donors, suggesting that the leukemic cells may have direct effects on normal T cells. Specifically, changes were noted in genes involved in Th1-induced differentiation ($CD4^+$ cells), as well as vesicle trafficking, cytoskeletal formation, and cytolytic enzymes ($CD8^+$ cells) [18]. Co-culture of CLL and normal cells showed that cell-to-cell interaction and cross-talk could cause adverse effects on the gene expression of normal cells, alluding again to the potential negative impact CLL cells may have on surrounding healthy cells in vivo [18].

In patients with CLL, there is an expansion of a subset of $CD8^+$ cytotoxic T cells with a $CD45RA^+$ $CD27^-$ phenotype that is often found in immunocompromised or cytomegalovirus (CMV)-seropositive individuals [16, 25] and thought to be involved in regulating CMV infection [3, 35]. Thus, in patients with CLL who are undergoing lymphocyte-depleting treatment regimens, the loss of $CD8^+$ cytotoxic T cells may provide a basis for the frequent episodes of CMV reactivation. There is also an increase in T regulatory cells in CLL, which may contribute to impaired T-cell function [2].

A number of factors have been identified that contribute to increased risk of infection in patients with CLL, including age, type and/or number of prior treatments, and immune cell status [21, 27, 36]. A retrospective analysis of 187 patients with CLL demonstrated that the number of chemotherapy ($p<0.001$), purine analogue ($p<0.001$), and monoclonal antibody treatments ($p=0.019$) significantly increased the risk for major infections [21]. Due to the chronic nature of CLL and subsequent disease relapses, most patients receive more than one treatment over the course of the malignancy. The cytotoxic effects of therapeutic regimens on normal immune cells result in greater patient susceptibility to infectious complications, and such risk increases as patients undergo each additional line of therapy. Patients may ultimately succumb to infections rather than malignancy. Patients with prior fludarabine treatment may be more susceptible to opportunistic infections due to the long-lasting effects of fludarabine on T cells, and up to 89% of these patients are at risk of developing severe infections [47].

Patients receiving first-line therapy for CLL are generally at a much lower risk of developing infections compared with those who have received multiple courses of prior therapy. Nevertheless, previously untreated patients may also be susceptible to infections due to hypogammaglobulinemia and the underlying malignancy [56]. Infections are less of a concern in younger patients, as shown in a recent study with frontline fludarabine-based treatment in which antibiotics or antiviral prophylaxes were not routinely used [11].

Recent studies have reported on the potential association between high-risk prognostic markers (e.g., elevated thymidine kinase, $CD38^+$ status, unmutated IgV_H status, and presence of genomic abnormalities) and an increased risk of developing infectious complications in patients with CLL [11, 15]. The utility of these biomarkers in clinical practice remains to be established.

Effect of alemtuzumab on immune cells

A rapid decrease in normal lymphoid and malignant CLL cells is readily apparent within a few weeks of alemtuzumab treatment. In the pivotal study of alemtuzumab in patients with relapsed/refractory disease, $CD19^+/CD5^+$ B cells and $CD3^+/CD4^+$ and $CD3^+/CD8^+$ T cells were significantly depressed after 4 weeks of treatment [30]; these findings were confirmed by another study that also noted a decrease in $CD16^+$ natural killer (NK) cells [49]. The T-cell population gradually recovered to baseline levels by 36 weeks after therapy initiation [30]. Similar results on the recovery of $CD4^+$ cells in alemtuzumab combination therapy were reported [12]. Importantly, several studies have shown that infectious events typically occur around the time of T-cell and neutrophil nadirs (Fig. 1) [13, 30, 38, 40, 49].

An array of immune cell populations was examined by flow cytometry at baseline and through 18 months following first-line alemtuzumab treatment [34]. $CD4^+$ and $CD8^+$ T cells, $CD3^-/56^+$NK cells, $CD3^+/56^+$NK T cells, and $CD19^+/5^-$ B cells were all profoundly decreased to <25% baseline through 9 months after treatment. Alemtuzumab also significantly depleted granulocytes and monocytes. The study showed that even lower cumulative doses of alemtuzumab could result in a sharp decrease in cell numbers for an extended period of time, although the cumulative dose level was not significantly associated with the extent or duration of lymphocyte depletion. There was, however, a trend toward lower levels of $CD4^+$ and $CD8^+$ T cells at the end of therapy in patients who received greater than median cumulative doses of alemtuzumab, although the actual bloodstream concentrations of alemtuzumab were not measured [34]. Interestingly, no late-occurring opportunistic infections or major infections were reported during unmaintained, long-term follow-up; this may partially be

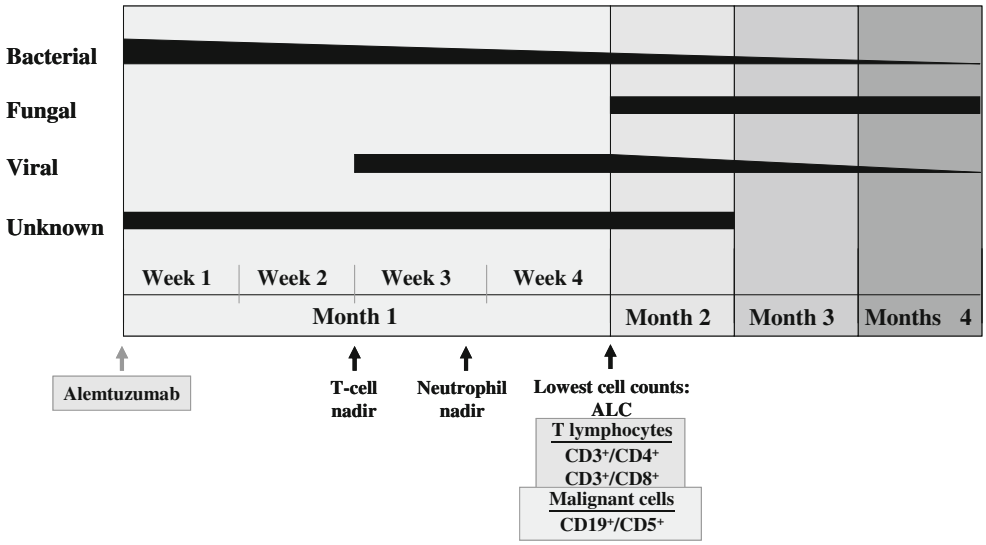

Fig. 1 Qualitative timeline of infections in conjunction with immune cell nadir in patients with relapsed/refractory CLL receiving alemtuzumab

explained by the patients' treatment-naive status prior to alemtuzumab therapy.

Alemtuzumab therapy is also known to cause transient neutropenia, anemia, and thrombocytopenia that resolve in most patients by a 2-month follow-up [30]. The effect of alemtuzumab on other blood cells such as macrophages has not been reported.

Infectious events associated with alemtuzumab therapy

Single-agent alemtuzumab therapy in first-line treatment of CLL

In general, infections associated with alemtuzumab therapy are less frequent in previously untreated patients than in patients with relapsed/refractory diseases. The infectious events in two studies of first-line alemtuzumab therapy are summarized in Table 1 [24, 33].

The recent phase III randomized CAM307 study compared first-line alemtuzumab administered intravenously versus chlorambucil administered orally [24]. Although grade 3/4 neutropenia was more common in the alemtuzumab arm, the incidence of grade 3/4 non-CMV infectious events was not significantly different between the two treatment arms (4.8% with alemtuzumab versus 2.7% with chlorambucil for febrile neutropenia; 3% and 1.4%, respectively, for bacteremia/sepsis). CMV events were more frequent in the alemtuzumab arm than in the chlorambucil arm. During treatment, 52.4% of patients receiving alemtuzumab had an asymptomatic positive CMV polymerase chain reaction (PCR), compared with 7.5% of patients receiving chlorambucil. No patient receiving chlorambucil had symptomatic CMV infection, whereas 15.6% of patients receiving alemtuzumab had symptomatic CMV infection without end organ involvement [24].

Single-agent alemtuzumab therapy in relapsed/refractory CLL

Infectious events in four published studies are summarized in Table 1. In an earlier study by Osterborg et al., patients who developed *Pneumocystis carinii* pneumonia (PCP) or septicemia tended to be more heavily pretreated or resistant to fludarabine treatment [46]. In another study in patients with relapsed or fludarabine-refractory CLL, infections were reported in 42% of patients, predominantly in the non-responder group. Seven of eight non-responders developed major infections during treatment and within 35 days following treatment completion, and two of them died from infections [49]. Similarly, in the pivotal study of 93 relapsed/refractory CLL patients, 25 patients (27%) experienced grade 3/4 infectious events (27%), which occurred more frequently in non-responders than in responders (36% versus 9.7%) [30]. In a recent study, 91 patients with relapsed/refractory CLL were treated with alemtuzumab until maximum response, which included achievement of minimal residual disease (MRD)-negative remission [38]. There were four infectious episodes in 18 MRD-negative patients, compared with 27 episodes in 73 patients who did not achieve MRD negativity. Collectively, these studies suggest a trend that infectious complications are more frequent in patients who are heavily pretreated or fludarabine-refractory and who do not respond or only partially respond to alemtuzumab therapy.

Alemtuzumab in combination therapy

In light of the promising single-agent activity of purine analogues and monoclonal antibodies in CLL, various chemoimmunotherapy combination regimens are currently under investigation in an effort to further improve patient outcomes. In a recent study, 36 patients with relapsed/

Table 1 Infectious events in single-agent alemtuzumab therapy

	Reference	Alemtuzumab therapy	Anti-infective prophylaxis	No. of patients	Neutropenia	CMV infection	Fungal infection	Bacterial infection	Viral infection (other than CMV)	Additional notes
First-line treatment	Lundin et al. [33]	30 mg SC 3 times a week	Valacyclovir, fluconazole, cotrimoxazole	38	Grade 4 in 21% patients	4 patients. One recovered spontaneously and three were successfully treated with ganciclovir administered intravenously	1 patient developed PCP (patient did not receive PCP prophylaxis due to allergy)	No major infection (>grade 1)	Not reported	No late-occurring infections during long-term unmaintained follow-up
	Hillmen et al. [24]	30 mg IV 3 times a week for up to 12 weeks (9.5% of patients with growth factor support)	TMS (double strength) famciclovir	147	Grade 3 or 4 in 41% of patients	15.6% symptomatic CMV infection; 52.4% asymptomatic positive CMV PCR	1 fatal *Candida albicans* (deemed unrelated to treatment)	3% bacteremia, 1.4% sepsis, tuberculosis (n=1), bronchopneumonia (n=1)	Not reported	4.8% febrile neutropenia
Treatment of relapsed/ refractory CLL	Osterborg et al. [46]	30 mg IV 3 times a week for up to 12 weeks	Acyclovir or TMS (optional, high-risk patients only)	29	21% grade 3, 20% grade 4	Not reported	Candidiasis given orally in 5 patients, PCP in 2 patients (both recovered after treatment)	4 non-PCP pneumonia, 4 septicemia (3 diagnosed, 1 suspected)	Localized HSV reactivation in 11 patients	No death during treatment and first 6 months follow-up
	Rai et al. [49]	30 mg IV 3 times a week for up to 16 weeks	Optional	24	Grade 3 or 4 in 21% of patients	1 suspected *Legionella*/ mycobacterium/ CMV infection	4 PCP (3 proven, 1 suspected), 1 *Candida*/ *Aspergillus*, 1 *Candida*, 1 invasive aspergillosis	1 *Klebsiella* pneumonia	Disseminated herpes zoster (1)	Severe infections were noted in 8% of patients at month 1, 6% at month 2, and 7% at month 3
	Keating et al. [30]	30 mg IV 3 times a week for up to 12 weeks	TMS Famciclovir	93	In 30% of patients during weeks 5–6. Resolved in the majority of patients by 2 months follow-up	7 cases, with 3 of grade 2 and 4 of grade 3	PCP (1), *Aspergillus* pneumonia (1), systemic candidiasis (1), pulmonary aspergillosis (1), invasive aspergillosis (1)	Septicemia (14, with 2 death)	Herpes simplex (6), herpes zoster (4)	Grade 3/4 infection: 10% in responders, 36% in non-responders
	Moreton et al. [38]	30 mg IV 3 times a week until maximum response	Cotrimoxazole, acyclovir	91	$<1\times10^9$/L in 48% of patients, $<0.5\times10^9$/L in 30% of patients	8 cases, with 2 of grade 1–2 and 6 of grade 3–4	Invasive pulmonary aspergillosis (2, 1 fatal), disseminated *Pseudoallescheria boydii* (1, fatal), probable invasive pulmonary fungal infection (2, 1 fatal), no PCP reported	Septicemia (11)	Herpes virus (5)	4 infectious episodes in 18 MRD-negative patients and 27 infectious episodes in 73 patients who did not achieve MRD negativity

refractory CLL were treated with fludarabine in combination with alemtuzumab (FluCam regimen: alemtuzumab 30 mg and fludarabine 30 mg/m^2 on three consecutive days administered every 28 days for up to 6 cycles) [12]. Most infections occurred within the first 3 months of treatment, when CD4$^+$ cells were at the lowest levels (Table 2). It is noteworthy that only two patients developed grade 3 subclinical CMV reactivation, which resolved with ganciclovir administered intravenously, although 80% of patients were CMV seropositive at baseline, suggesting that the rate of CMV reactivation might be lower with this 4-weekly combination regimen. Overall, patients who developed severe infectious complications were those who experienced progressive disease after FluCam therapy.

The combination of alemtuzumab and steroid methylprednisolone was also investigated in patients with relapsed/refractory CLL [48]. This regimen consists of methylprednisolone 1.0 g/m^2 administered intravenously on days 1–5 and alemtuzumab 30 mg thrice weekly in a 28-day cycle for up to 4 cycles. Five patients with p53 defects were treated with this regimen. All five patients experienced infections that included CMV reactivation, suspected pulmonary aspergillosis, bacterial chest infection, and bacterial sinusitis, but all infections were successfully treated. The high infection rate was not unexpected, because four of the five patients were already at high risk of infection prior to therapy.

Alemtuzumab in consolidation therapy

Several studies have evaluated alemtuzumab as consolidation therapy after initial response to induction chemotherapy (Table 2). The rationale is that reduction in residual disease by alemtuzumab may improve patient response and survival. Indeed, an impressive improvement in progression-free survival was demonstrated with alemtuzumab consolidation [54, 61]. However, elevated infectious complications have also been noted in some studies [32, 61]. For example, the earlier CLL4B trial of the German CLL Study Group had to be stopped due to severe infection in seven of 11 patients [61]. In particular, the CALGB 10101 study reported six infection-related deaths in patients receiving alemtuzumab consolidation after fludarabine/rituximab induction therapy [32]. It is not immediately clear why infection-related mortality is higher in this trial than in other consolidation trials [37, 43, 61]. An open issue concerning alemtuzumab consolidation therapy is whether the alemtuzumab dosage should be adjusted according to the level of residual disease after induction therapy. If a patient is already in MRD-negative remission, it is probably not desirable to administer alemtuzumab at the full dose of 30 mg three times a week. We speculate that the treatment regimen in these trials may have been too intense and/or administered too early following induction chemotherapy, therefore resulting in excessive immunosuppression and increased infection.

To establish a dosing schedule that would maintain clinical efficacy of consolidation therapy while minimizing infectious complications, the German CLL Study Group recently conducted a phase I/II dose-escalation trial (CLL2I) to determine the maximum tolerated dose (MTD) of alemtuzumab consolidation in patients after second-line chemotherapy. The MTD of alemtuzumab consolidation administered intravenously was determined to be 10 mg once weekly, which was well tolerated, with no severe toxicity, no severe infections, and no clinically symptomatic CMV reactivation. Four patients had converted from PR to CR after consolidation and nine of 12 patients had a reduction in their MRD levels, suggesting that lower-dose alemtuzumab consolidation therapy is both safe and effective [14].

Alemtuzumab in SCT

Patients undergoing SCT are at a high risk of developing infections throughout different procedural stages—pretransplantation conditioning through posttransplantation follow-up [31]. This susceptibility may be influenced by a patient's underlying disease, conditioning therapy, presence of graft-versus-host disease (GvHD), or conformity between the donor and recipient's human leukocyte antigen. During the conditioning phase, patients are likely to develop treatment-related neutropenia, which adds to the high risk of developing infections within the first 30 days of treatment, including herpes simplex virus (HSV), CMV, Gram-negative bacteria, *Staphylococcus* spp., *Enterococcus* spp., *Candida* spp., and *Aspergillus* spp. During the postengraftment period, patients are susceptible to CMV reactivation, *P. jiroveci*, and *Toxoplasma gondii* at 30 to 100 days and varicella zoster virus (VZV) and encapsulated bacteria at >100 days. Respiratory and enteritic viruses may be present throughout all phases.

The Campath series of antibodies was initially developed to deplete T cells, and early studies demonstrated its ability to provide durable engraftment and to reduce GvHD [19, 20, 58]. Recent studies confirmed that the incorporation of alemtuzumab into non-myeloablative conditioning regimens reduced the occurrence of GvHD and associated mortality in patients undergoing allogeneic SCT [5, 6]. Alemtuzumab-based conditioning (with fludarabine and melphalan) prior to allogeneic transplantation in 41 young patients (<70 years of age) with advanced CLL showed reduced acute and chronic GvHD, with a 10% GvHD-related mortality rate [10]. Patients received antifungal (fluconazole or itraconazole), acyclovir, and trimethoprim and sulfamethoxazole (TMS) (or alternatively, dapsone or

Table 2 Infectious events in alemtuzumab combination and consolidation therapy

	Reference	Alemtuzumab therapy	Anti-infective prophylaxis	No. of patients	Neutropenia	CMV infection	Fungal infection	Bacterial infection	Viral infection (other than CMV)	Additional notes
Combination therapy	Elter et al. [12]	30 mg IV in combination with fludarabine 30 mg/m^2/day on the first 3 days of a 28 day cycle, in patients with relapse/refractory CLL	TMS, valacyclovir	36	Grade 1–2 in 25% patients, grade 3–4 in 26% of patients	2 grade 3 infections	*Aspergillus* pneumonia (2, both in patients with PD)	*Escherichia coli* sepsis (after CMV infection, fatal), *Pseudomonas aeruginosa* (1)	Not reported	Grade 3/4 infection was reported in 4 patients (11%), and 2 of the 3 patients with grade 4 infections were refractory to prior therapy and to FluCam
Consolidation therapy	O'Brien et al. [42]	10 or 30 mg IV 3 times a week for 4 weeks, in patients with relapse/refractory CLL	TMS, valacyclovir	41	Grade 3–4 in 71% at 30 mg level versus 17% at 10 mg level	9 symptomatic CMV reactivation (1 fatal due to CMV hepatitis). None of 4 patients with ganciclovir prophylaxis develop CMV reactivation	Not reported	Septicemia (1), *Listeria* (1)	Viral myocarditis (1), influenza A (1)	One case each of pneumonia of unknown origin and sinusitis. One patient with CMV reactivation also had concomitant EBV and large cell lymphoma and died
	Wendtner et al. [61]	30 mg IV 3 times a week after a median of 67 days following first-line F or FC therapy	Cotrimoxazole, famciclovir	11	Grade 3 in 4 patients, Grade 4 in 3 patients	4 cases of grade 3 infection	Grade 4 pulmonary aspergillosis (1)	Reactivation of pulmonary tuberculosis (1)	HSV/HHV-6 (1), herpes zoster (1)	Trial had to be stopped due to sever infection in 7 of 11 patients. No death was reported
	Montillo et al. [37]	10 mg SC 3 times a week for 6 weeks after a median of 16 weeks following fludarabine-based first-line therapy	Cotrimoxazole, acyclovir	34	No hematologic toxicity observed	CMV reactivation in 18 patients	No documented fungal infection	No documented bacterial infection	Not reported	
	Lin et al. [32]	30 mg SC 3 times a week for 6 weeks after 4 months following first-line FR therapy	Standard PCP and varicella zoster prophylaxis	51	Not reported	3 cases in 34 patients with PR, 3 cases in 17 patients with CR (1 fatal)	4 cases in patients with PR, 1 PCP in patients with CR (fatal)	*Cryptococcus* (1), *Listeria* meningitis (1, fatal) and *Legionella* pneumonia (1, fatal) in patients with CR	1 viral meningitis (fatal) in patients with CR, 1 EBV lymphoproliferative disorder (fatal)	1 hemorrhagic cystitis
	Fischer et al. [14]	Dose escalation trial, IV or SC once weekly for 8 weeks after 90–150 days following second-line F/FC/FCR therapy (CLL2I protocol of GCLLSG)	Trimethoprim/cotrimoxazole Valacyclovir	6 at 10 mg IV, 4 at 20 mg IV, 2 at 10 mg SC	Not reported	2 subclinical CMV reactivation	No severe infection observed	No severe infection observed	No severe infection observed	2 DLT at 20 mg IV: 1 FUO, 1 exacerbated erythema exsudativum multiforme. MTD of alemtuzumab administered intravenously was determined as 10 mg once weekly. MTD of alemtuzumab administered subcutaneously has yet to be determined

pentamidine) prophylaxis. Treatment- or GvHD-related mortality from infectious complications was caused by pulmonary aspergillosis (two patients), bacterial pneumonia (two patients), neutropenic sepsis (two patients), respiratory syncytial virus (RSV) pneumonia (one patient), EBV-related posttransplantation lymphoproliferative disease (one patient), and fungal cerebral abscess (one patient). Non-lethal infections were mainly viral and fungal, with 68% of patients at risk for CMV reactivation, two of whom were treated for CMV.

Alemtuzumab therapy may not be beneficial in combination with total body irradiation in the autologous SCT setting. In the CLL3C trial, patients received high-dose alemtuzumab and total body irradiation prior to autologous SCT [64]. Compared with the CLL3 trial, in which a similar treatment regimen was given without alemtuzumab, the CLL3C trial reported a high incidence of GvHD-like syndrome, high non-relapse-related mortality and a wide array of infectious complications (including CMV, herpes zoster, VZV, and pneumonia), despite improved disease control at the molecular level.

Management of infectious events associated with alemtuzumab therapy

In this section, we discuss some well-established practical recommendations that are based on previous clinical experiences.

Timeline of alemtuzumab-associated infections

A qualitative timeline (Fig. 1) [29, 30] shows that bacterial infections appear mainly during the first weeks of alemtuzumab treatment and become less frequent during subsequent weeks of treatment; viral infections, particularly CMV reactivation, were evident beginning in week 3 and generally tapered off over time; and fungal infections were mainly evident during the posttreatment phase of alemtuzumab. Unknown (or unclassified) infectious episodes were seen mainly during and just after treatment and may include fever of unknown origin (FUO).

Monitoring, prophylaxis, and treatment of infection

Before initiating alemtuzumab treatment, baseline status should be evaluated through examination of overall physical characteristics; computed tomography (CT) or ultrasound scan of enlarged and potentially palpable lymph nodes, liver, or spleen (where indicated); assessment of comorbid disease; serological status of hepatitis B, hepatitis C, CMV, HSV, VZV, EBV, and HIV; and complete blood counts [45]. The strategy of infection monitoring and prophylaxis must always consider these baseline findings and other risk factors from the patient's medical history, such as age, comorbid diseases, and earlier infections.

The following prophylactic practices were recommended for patients receiving alemtuzumab: TMS (160 mg trimethoprim, 800 mg sulfamethoxazole) BID (or alternatively, aerosolized pentamidine, dapsone administered orally, and atovaquone given orally) for prevention of PCP; and acyclovir, famciclovir, or valacyclovir as antiviral prophylaxis for at least 2 months after completion of therapy (or more conservatively, 4 months after therapy or until $CD4^+$ counts recover to at least 250/μL; Table 3) [26, 29]. Prophylaxis with valganciclovir has been shown to be effective in preventing the onset of symptomatic CMV reactivation in a randomized trial [42] and should be considered at the discretion of attending physicians.

Broad-spectrum antibacterial prophylaxis should be avoided because it offers no improvement in mortality, has the potential to select for resistant bacterial strains, and frequently causes adverse events such as hypersensitivity or *Clostridium difficile*-associated diarrhea [1]. Prophylactic TMS may provide some antibacterial activity, although it primarily targets PCP.

Routine antifungal prophylaxis is also not recommended. The results of evidence-based trials suggest the use of fluconazole 400 mg/day administered orally as antifungal prophylaxis only in allogeneic SCT, but not in conventional chemo- or immunotherapy. Posaconazole was proven effective in preventing fungal infections and death in long-term neutropenic patients and in patients with GvHD after allogeneic SCT [9, 57]; however, the dosage needed to treat patients receiving alemtuzumab remains unknown and the substance has not yet been tested in this setting. Similarly, little evidence is available to support the prophylactic use of itraconazole or liposomal amphotericin [7]. It is important to note that agents such as fluconazole will not protect against filamentous fungi (i.e., *Aspergillus* spp.). In patients experiencing prolonged FUO (>72 h) in whom CMV reactivation has been ruled out as a cause of fever, pulmonary high-resolution or thoracic CT should be performed [4, 23]. Early treatment with caspofungin (70 mg loading dose followed by 50 mg QD) or liposomal amphotericin B (3 mg/kg QD) may be clinically warranted [59]. In the event of probable (measured by two positive serum galactomannan samples or halo signs in pulmonary CT scan per modified European Organization for Research and Treatment of Cancer [EORTC]/Mycoses Study Group [MSG] criteria) or proven invasive aspergillosis, the treatment of choice is voriconazole 6 mg/kg loading dose followed by 4 mg/kg BID, as recommended by the Infectious Disease Society of America (IDSA) [22].

Antiviral prophylaxis is generally not recommended in the SCT setting if the donor and recipient are seronegative

Table 3 Prophylaxis strategies for common infections associated with alemtuzumab therapy

Infection types	CLL	Allogeneic transplantation
Bacterial		
Staphylococcus aureus	Broad-spectrum antibacterial prophylaxis not recommended	Broad-spectrum antibacterial prophylaxis not recommended
Other Gram-positive bacteria		
Mycobacterium tuberculosis		
Septicemia		
Fungal		
Aspergillosis	General antifungal prophylaxis not recommended	Fluconazole 400 mg QD
Cryptococcus	PCP[a]: trimethoprim/sulfamethoxazole[b]	
Pneumocystis jiroveci (formerly *P. carinii*) pneumonia (PCP)		
Systemic candidiasis	Prophylaxis for high-risk patients: fluconazole 50 mg QD or itraconazole 5 mg/kg QD PO	
Viral		
Cytomegalovirus (CMV)	CMV prophylaxis in early development	CMV prophylaxis not recommended Preemptive therapy[c]: ganciclovir 5 mg/kg daily or ID or foscarnet 60 mg/kg TID or valacyclovir 250–500 mg BID PO
Herpes simplex virus (HSV)	Acyclovir 200–400 mg TID PO or famciclovir 500 mg BID or valacyclovir 250–500 mg BID PO[d]	Acyclovir 400 mg QD or TID (HSV)[e]
Varicella zoster virus (VZV)		
Epstein–Barr virus (EBV)	Prophylaxis for EBV or HBV not recommended	Lamivudine 100 mg (HBV)[f]
Hepatitis B virus (HBV)		

Data from [7, 29, 53]

BID Twice daily, *DS* double strength, *PO* oral, *QD* once daily, *TID* three times daily

[a] Prophylaxis begins at onset of alemtuzumab therapy through ≥6 months posttherapy or $>0.25\times10^9$ $CD4^+$ cells/L.

[b] Dose and schedule determined according to local standards (i.e., double-strength BID); alternative prophylaxis is dapsone 100 mg 5 days/week PO, nebulized pentamidine 300 mg/month, or atovaquone 750 mg BID PO.

[c] Initiated following an increase of viremia as determined by viral antigen or polymerase chain reaction.

[d] Prophylaxis begins 1 week prior to 2 months posttherapy.

[e] Only if donor or recipient is seropositive.

[f] Only if recipient is HBs-Ag- or anti-HBc-positive.

for viral titers. Prophylaxis for HSV/VZV is not recommended unless the patient is seropositive and has additional risk factors including low CD4 count (<50/μL), previous corticosteroid or fludarabine treatment, a background of recurring herpes infections, or total body irradiation during conditioning [53]. Acyclovir 400 mg QD or three times per day (TID) is recommended if the donor or recipient is HSV seropositive. Acyclovir or valacyclovir both have similar prophylactic efficacy for patients with hematological malignancies [60]. For patients who are seropositive for hepatitis B virus, lamivudine 100 mg/day is recommended as prophylaxis, although it has the potential to enhance the risk of developing hepatitis B-resistant viral strains [53].

Treatment of infections

In instances of fever, the patient needs to be examined for bacterial, fungal, or viral infections using monitoring techniques outlined in Table 4. Early blood cultures and start of empirical antibiotic treatment are especially imperative in severely immunosuppressed patients. Efforts to identify the source of infection should always be undertaken.

The timing of serious infections may be anticipated using the timeline discussed above (Fig. 1). Upon examining the types of bacteria present in alemtuzumab-treated patients, it was found that 60% to 70% of bacterial infections are caused by Gram-positive bacteria [47]. In immunocompromised patients, empiric antibiotic treatment should be started immediately after the onset of infection to treat Gram-positive and Gram-negative bacteria (including *Pseudomonas* spp.). Empirical treatment should consider frequently isolated pathogens of the hospital environment and their resistances. In patients experiencing prolonged FUO (>48 h), pulmonary high-resolution or spiral CT should be performed [4, 23]. Early treatment with caspofungin (70 mg loading dose followed by 50 mg QD) or liposomal amphotericin B (3 mg/kg QD) may be clinically warranted in high-risk patients [59]. In the event of probable (measured by two positive serum galactomannan samples or halo signs in pulmonary CT scan per modified

Table 4 Patient monitoring techniques

Bacterial	Chest X-ray[a]
	Microbiologic cultures[a]
	Bronchoalveolar lavage[b]
Fungal	Sputum swab/nasal culture[a]
	Serum galactomannan[a]
	CT scan of chest/sinuses[c]
	Bronchoalveolar lavage (galactomannan, culture)[b]
Viral	Serologic baseline screen (CMV IgM & IgG, hepatitis B and C, HIV, HSV, VZV)[d]
	CMV IgG positive: frequent PCR or antigenemia tests[e]

CMV Cytomegalovirus, *CT* computed tomography, *HIV* human immunodeficiency virus, *HSV* herpes simplex virus, *IgG* or *IgM* immunoglobulin G or M, *PCR* polymerase chain reaction, *VZV* varicella zoster virus

[a] In case of fever/infection

[b] If deemed necessary

[c] For patients with previous history of fungal infection or fever of unknown origin >72 to 96 h and in case of lung infiltrates

[d] At baseline

[e] In patients with positive CMV IgG at baseline or any patient with fever

EORTC/MSG criteria) or proven invasive aspergillosis, the treatment of choice is voriconazole 6 mg/kg loading dose followed by 4 mg/kg BID, as recommended by IDSA [22]. Another well-established treatment choice is liposomal amphotericin B 3 mg/kg QD [8].

Management of CMV reactivation and disease

CMV reactivation is the most common opportunistic infection observed in alemtuzumab-treated patients, although CMV-related organ disease or death is rare. Early detection of symptomatic reactivation, along with increased awareness of monitoring techniques and the use of preemptive therapy, has largely improved the management of CMV reactivation. This is evident in the recent report by Montillo and colleagues, in which active CMV infection was prevented with preemptive ganciclovir therapy (or by spontaneous resolution) in patients who developed CMV reactivation [37].

CMV reactivation typically occurs between weeks 3 and 8 of alemtuzumab treatment, around the time of or shortly after T-cell nadir [30, 38, 40]. Routine CMV-specific prophylaxis is not recommended due to lack of data from large randomized studies. Patients should be closely monitored for CMV reactivation using antigenemia testing (pp65 and pp67) and/or PCR throughout the treatment and follow-up periods, particularly in those who are CMV seropositive at baseline (Table 5) [29]. Intervals between CMV testing may be increased after the second month of therapy, but patients presenting with FUO should be tested promptly, because FUO (≥38°C or 101°F) may signal CMV reactivation (even in a patient who is CMV negative at baseline). A recently updated guideline on the management of CMV recommends that alemtuzumab therapy should be held only when patients have persistent, symptomatic CMV reactivation [44]. If a patient is CMV positive for two consecutive tests but remains asymptomatic, ganciclovir to be administered orally is recommended and alemtuzumab treatment should be continued. In symptomatic cases, ganciclovir (5 mg/kg BID) should be administered as first-line treatment for 14 to 21 days and alemtuzumab should be paused until negative CMV status is achieved. Foscarnet (60 mg/kg TID) may be added in the event of

Table 5 Guidelines for monitoring CMV status during alemtuzumab therapy in CMV IgG-positive patients at baseline

Patient status	Recommendation
FUO	Test for CMV via PCR/antigenemia (in both CMV positive and negative patients)
Persistent FUO, no testing available	Treat empirically with ganciclovir
CMV negative, asymptomatic	Monitor CMV status by weekly or biweekly PCR/antigenemia testing
CMV negative, pulmonary infection	Perform bronchoscopy and lavage to test for other pathogens If unresponsive to antibiotics (or test is negative for other pathogens), treat with ganciclovir for 14–21 days
CMV positive, asymptomatic	Monitor for symptoms If CMV positive for 2 consecutive tests, begin preemptive therapy with oral ganciclovir or equivalent for 7–14 days Continue alemtuzumab therapy
CMV positive, symptomatics	Treat with i.v. ganciclovir or equivalent for 14–21 days If persistently symptomatic, hold alemtuzumab until asymptomatic and CMV negative Perform bronchoscopy and lavage if symptomatic for pulmonary infection

CMV Cytomegalovirus, *FUO* fever of unknown origin, *PCR* polymerase chain reaction

clinical CMV disease or substituted for ganciclovir if patients remain unresponsive or minimally responsive to ganciclovir treatment [40, 44].

Conclusions

The broad umbrella of infections present in patients with CLL reaffirms the need to closely monitor and manage infectious events beginning at treatment initiation. Various factors contribute to the development of infectious events in patients with CLL, including increased susceptibility due to immune defects inherent to the disease process itself, as well as the immunosuppressive effects of therapeutic regimens. Because of its promising efficacy, both as a single agent and in combination therapy, alemtuzumab is emerging as an important component of therapeutic regimens for CLL. A major complication of alemtuzumab therapy is infection that is predictable and manageable but also potentially severe and life-threatening if left undetected or untreated. As this agent is being used more and more widely, it is critical that infectious complications be managed with vigilance to minimize infection-related mortality and maximize therapeutic benefit.

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