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Spectrum of infection, risk and recommendations for prophylaxis and screening among patients with lymphoproliferative disorders treated with alemtuzumab*

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Summary

There is an increasing use of monoclonal antibodies in the treatment of haematological malignancies. Alemtuzumab (Campath-1H; Ilex Pharmaceuticals, San Antonio, TX, USA) is a monoclonal antibody reactive with the CD52 antigen used as first and second line therapy for two types of lymphoproliferative disorders: chronic lymphocytic leukaemia (CLL), and T-cell lymphomas [both peripheral (PTCL) and cutaneous (CTCL)]. With alemtuzumab therapy, viral, bacterial and fungal infectious complications are frequent, and may be life threatening. An understanding of the patients at highest risk and duration of risk are important in developing recommendations for empirical management, antimicrobial prophylaxis and targeted surveillance. This review discusses the infection risks associated with these lymphoproliferative disorders and their treatment, and provide detailed recommendations for screening and prophylaxis.

Keywords: alemtuzumab, infection risk, prophylaxis, lymphoproliferative disorders, screening.

Effects of alemtuzumab on immunity

The mechanism of action of alemtuzumab and the associated pattern of immune reconstitution may provide an understanding of the spectrum of opportunistic infections seen. Alemtuzumab binds to 95% of normal human blood-lymphocytes as well as malignant B- and T-cell lymphocytes (Salisbury *et al*, 1994). Malignant T cells express the CD52 antigen in high density and the intensity of the expression appears to be correlated with clinical effects (Ginaldi *et al*, 1998). There is a profound and long-lasting depletion of mature B- and T-lymphocytes, natural killer cells and monocytes (Lundin *et al*, 2004). The majority of treated patients manifest a profound peripheral blood lymphopenia by 2–4 weeks that may persist for over 1 year (Dearden *et al*, 2001; Rawstron *et al*, 2004). In a study of immune reconstitution in 23 patients with B-cell chronic lymphocytic leukaemia (B-CLL) who received alemtuzumab as first line therapy, the median peripheral blood $CD4^+$ and $CD8^+$ lymphocyte counts remained at <25% of baseline beyond 9 months from completion of therapy (Lundin *et al*, 2004). When alemtuzumab was used *in vivo* to deplete donor $CD52^+$ cells from the stem-cell graft, recipients remained lymphopenic for 2 months post-transplantation with $CD4^+$ lymphocyte recovery delayed until 9 months (Faulkner *et al*, 2004). In patients receiving alemtuzumab for the treatment of CLL, neutropenia of $0{\cdot}5 \times 10^9$/l is observed in up to a third of patients, occurs at around 4 weeks of therapy, but usually recovers within 2–3 weeks (Keating *et al*, 2004). In a series of patients with cutaneous T-cell lymphoma (CTCL), neutropenia occurred in 8 of 11 patients (73%) between 2 and 12 weeks of treatment with variable duration lasting months in severe cases (Gibbs *et al*, 2005).

Infection rates in CLL

Patients with CLL have impaired humoral and cellular immunity (CMI), defects in the complement systems and variable neutropenia, depending on marrow infiltrates that contribute to the high rate of infections (Ravandi *et al*, 2003). Hypogammaglobulinaemia and advanced disease are major predisposing factors. It is estimated that up to 50% of patients have recurrent infections (Ravandi *et al*, 2003). The 5-year risk for severe infection was 26% in one cohort of 125 patients analysed over 10 years (Molica *et al*, 1993).

Bacterial infections are the principal risk in patients treated with conventional therapies. Opportunistic infections such as *Pneumocystis jirovecii* (previously called *P. carinii*) are

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uncommon, as are tuberculosis and fungal infections as the result of the relative preservation of CMI early in the disease (Ravandi *et al*, 2003).

Infection risk is increased following purine analogue (fludarabine and cladribine) therapy because of the side effects of myelosuppression and marked lymphopaenia. The proportion of patients with grade 3 or 4 infection is 6–45% depending on extent of prior treatment, disease status and response to therapy (Ravandi *et al*, 2003; Tam *et al*, 2004). Gram-positive infections and herpes virus infections (including varicella-zoster virus, VZV) occur more frequently than with conventional therapies (Morrison *et al*, 2001). Patients with fludarabine resistant or partially responsive disease are at highest risk of infection (Perkins *et al*, 2002). The addition of the anti-B-cell antibody rituximab to nucleoside analogue-based therapy does not appear to increase the risk of early or late infections (Keating *et al*, 2005; Tam *et al*, 2005).

The relative risk of infections related to cell-mediated immunity deficit is greatly increased when fludarabine is combined with corticosteroids (Anaissie *et al*, 1998). However, the addition of other non-steroid cytotoxic agents, such as cyclophosphamide, with or without mitoxantrone, at a lower total fludarabine than used as a single-agent does not measurably increase the infection risk above full-dose single agent fludarabine alone (Bosch *et al*, 2005; Eichhorst *et al*, 2005). Although there are reports of *P. jirovecii* pneumonia and other fungal infections, listeriosis, mycobacterial infections, *Respiratory syncytial* and herpes virus infections and primary multifocal leucoencephalopathy occurring in heavily pretreated patients receiving these combinations, this may reflect the cumulative effects of numerous therapies (O'Brien *et al*, 2001; Ravandi *et al*, 2003; Tam *et al*, 2004).

All but one published study of alemtuzumab therapy in B-CLL have included patients who were previously treated with purine analogues or alkylating agents (Table I). Most studies used a regimen in which alemtuzumab was given 30 mg thrice weekly for at least 12 weeks if tolerated. In pretreated patients the reported risk of infections ranged from 23% to 79% (Cavalli-Bjorkman *et al*, 2002; Kennedy & Hillmen, 2002; Rai *et al*, 2002; Laurenti *et al*, 2004; Rawstron *et al*, 2004; Rieger *et al*, 2004; Wendtner *et al*, 2004; Lin *et al*, 2005). In contrast, only 2/23 (8·7%) of B-CLL patients receiving alemtuzumab as first line single agent therapy had an infection during the follow-up period of 24 months (Lundin *et al*, 2002).

As observed with purine analogue therapy, response to alemtuzumab appears to be related to the risk of infection (Keating *et al*, 1998; Keating *et al*, 2002). Non-responders to alemtuzumab had an increased risk of severe infection (36% vs. 10%, $P < 0{\cdot}01$) in the largest study of the use of alemtuzumab in patients with pretreated B-CLL (Keating *et al*, 2002).

Thus pretreated patients, particularly those who received a purine analogue alone or in combination, and those with advanced stage and not responding to alemtuzumab therapy appear to be at highest risk for infectious complications.

Table I. Infections observed in clinical studies of alemtuzumab in chronic lymphocytic leukaemia (CLL; total number of patients treated = 222) and peripheral and cutaneous lymphomas/leukaemia's (CTCL; total number of patients treated = 135).

Reported infection type	CLL *n*(%)*	CTCL *n*(%)†
Viral infections	38 (44·7)	37 (43·0)
CMV	24	23
HSV	7	6
VZV	2	4
HSV6	1	0
EBV-related	3	2
Parvovirus	0	1
Influenza	1	1
Bacterial infections	29 (34·1)	34 (39·5)
Septicaemia	16	17
Pneumonia	11	5
Meningitis	1 (listeria)	0
TB	1	2 (1 miliary)
Cellulitis	0	4
PUO	NR	6
Fungal infections	18 (21·1)	15 (17·5)
PCP	7	2
Aspergillosis	7	7
Systemic candidiasis	2	2
Zygomycosis	1	1
Cryptococcus	1 (pneumonia)	1 (meningitis)
Fusarium	0	1
Scedosporium	0	1
Total	85	86

Clinical trials with a minimum of 10 patients were included.
*CLL studies (Cavalli-Bjorkman *et al*, 2002; Kennedy & Hillmen, 2002; Lundin *et al*, 2002; Rai *et al*, 2002; Laurenti *et al*, 2004; Rawstron *et al*, 2004; Rieger *et al*, 2004; Wendtner *et al*, 2004; Lin *et al*, 2005). Median number of patients = 23 (range 11–93).
†CTCL studies: (Dearden *et al*, 2002; Kennedy *et al*, 2003; Lundin *et al*, 2003; Enblad *et al*, 2004; Gibbs *et al*, 2005). Median no. patients 22 (range 11–50).
CMV, cytomegalovirus; HSV, herpes simplex virus; VZV, varicella-zoster virus; EBV, Epstein–Barr virus; TB, tuberculosis; PUO, pyrexia of unknown origin; PCP, *Pneumocystis jirovecii* pneumonia.

Although the majority of infections occurred within the first 3 months of commencing treatment, some infections were reported up to 180 d post-treatment including *Mycobacterium tuberculosis*, invasive fungal infections and *Herpes zoster* (Keating *et al*, 2002). The potential for late infections in the higher risk patient group must be considered when considering duration of prophylaxis.

Infection rates in patients with cutaneous T-cell lymphoma (CTCL)

Bacterial sepsis is the most common infectious complication of CTCL and is the ultimate cause of about 50% of deaths from CTCL (Posner *et al*, 1981; Dalton *et al*, 1997). Axelrod *et al* (1992) retrospectively studied 356 patients with CTCL in the

era predating monoclonal antibodies and identified 478 infective episodes. Cutaneous bacterial infection was most common, followed by cutaneous *Herpes simplex* virus (HSV) and VZV infection, bacteraemia, bacterial pneumonia and urinary tract infection. Overall, the incidence of bacterial infections (23·3 per 100 patient-years) was greater than viral, fungal and parasitic infections (4·1, 0·5 and 0·3 per 100 patient-years respectively).

Disruption to the normal skin barrier by tumour infiltration, skin biopsies, intravenous catheter placement and local skin infection are frequent portals of entry for bacteraemia (Tsambiras *et al*, 2001). Infection risk is increased with advanced disease as well as combination chemotherapies (methotrexate/alkylating agents) (Axelrod *et al*, 1992; Akpek *et al*, 1999).

Staphylococcus aureus is the most common bacterial pathogen (Posner *et al*, 1981; Axelrod *et al*, 1992). Infections with *P. jirovecii*, *Toxoplasma gondii*, *Nocardia* spp., *M. tuberculosis* and mucosal infection with *Candida* species have also been reported (Axelrod *et al*, 1992; Foss *et al*, 1994; Akpek *et al*, 1999; Enomoto *et al*, 2002). Patients infected with human T-cell lymphotropic virus-1 (HTLV-1) are at increased risk of infection with *Strongyloides stercoralis*, and possibly with *M. tuberculosis* and leprosy (Marsh, 1996).

In studies of alemtuzumab for CTCL, the patients were all pretreated. The combined infection rate for the reported studies was 63·7% (Dearden *et al*, 2002; Kennedy *et al*, 2003; Lundin *et al*, 2003; Enblad *et al*, 2004; Gibbs *et al*, 2005). Bacterial infection accounted for 39·5% of all infectious episodes with half of these related to septicaemias. Cytomegalovirus (CMV) reactivation was the most common viral infection followed by HSV and VZV. A recent study examining the use of low dose alemtuzumab in 10 patients reported only 1 episode of CMV reactivation (10%; Zinzani *et al*, 2005). We have previously reported a case of red-cell aplasia because of parvovirus B19 infection in a patient with mycoses fungoides treated with alemtuzumab (Herbert *et al*, 2003). Fungal infections were also seen at a high frequency in this patient group occurring in 17·5% of treated patients. Importantly, 10 of the 15 reported fungal infections were because of moulds.

Recommendations

The manufacturer (Ilex Pharmaceuticals, San Antonio, TX, USA) clearly warns the prescriber that serious bacterial, viral, fungal and protozoal infections have been reported and that deaths have occurred. Prophylaxis for *P. jirovecii* pneumonia and herpes-related infections is recommended at the onset of treatment to continue for a minimum of 2 months from the last dose of alemtuzumab or until the CD4 counts are $>0{\cdot}200 \times 10^9$/l.

A summary of our recommendations for surveillance and prophylaxis of important bacterial, viral and fungal infections in patients receiving alemtuzumab is shown in Table II. Other considerations, such as geographic location and epidemiological risk-factors (for diseases such as tuberculosis), should alert the clinician to perform the appropriate screening tests prior to commencement of treatment. The duration of prophylaxis should take into account the individual's risk for infection based on stage of disease, number of prior therapies, response to alemtuzumab therapy and immune reconstitution. Detailed recommendations for viral, bacterial, mycobacterial, fungal and tropical infections are described in the following sections.

P. jirovecii pneumonia prophylaxis

Pneumocystis jirovecii pneumonia has been observed, largely where prophylaxis has not been administered (Rieger *et al*, 2004) (Rai *et al*, 2002) or tolerated (Lundin *et al*, 2002). Prophylaxis should be administered for all patients receiving alemtuzumab, and continued for a minimum of 6 months after cessation of therapy (Oscier *et al*, 2004).

If trimethoprim-sulphamethoxazole is not tolerated or is contraindicated, a second-line prophylactic agent should be used. Suitable second-line agents include: dapsone, pentamidine, or atovaquone. Of note, dapsone (Souza *et al*, 1999) and pentamidine (Vasconcelles *et al*, 2000) have demonstrated inferiority when compared with trimethoprim-sulphamethoxazole for prophylaxis following bone marrow transplantation and although atovaquone has been safely administered following autologous stem-cell transplantation (Colby *et al*, 1999), studies of efficacy in the haematology population are lacking. In the absence of controlled trials comparing these agents, route of administration, costs and local availability must also be considered.

Antiviral prophylaxis

All clinical studies of alemtuzumab included antiviral prophylaxis (acyclovir, famciclovir or valacyclovir) for herpes viruses for at least 2 months after completion of therapy using standard prophylaxis doses for HSV/VZV, rather than the high doses used to prevent CMV. This has reduced but not eliminated the risk of severe HSV and VZV infections, and appears to delay events until after cessation of prophylaxis.

Cytomegalovirus reactivation, as measured by positive plasma polymerase chain reaction (PCR) for CMV DNA, is the most common opportunistic infection and is reported in 15–66% of patients (Nguyen *et al*, 2002; Laurenti *et al*, 2004; Gibbs *et al*, 2005). However, the natural history of CMV DNAemia is not well described (Laurenti *et al*, 2004; Seymour *et al*, 2004). The kinetics of CMV viral load, such as rate of rise, number of copies/ml of plasma and relationship of persistently positive serial tests in relation to risk for CMV disease are not known. All CMV infections occurred early during the first 3 months of alemtuzumab therapy when CD4 and CD8 cell counts were profoundly suppressed (Keating *et al*, 2002). Deaths because of CMV pneumonia (Enblad *et al*, 2004; Lin *et al*, 2005) and hepatitis (O'Brien *et al*, 2003) have been reported. Without prophylaxis in patients with lymphoid

Table II. Recommendations for surveillance, anti-infective prophylaxis and treatment in patients with lymphoproliferative disorders treated with alemtuzumab.

Infection	Surveillance strategy	Drug treatment or prophylaxis (dose)	Duration*
Viral			
Cytomegalovirus (CMV)	Baseline CMV serology prior to therapy CMV screened or filtered blood for CMV seronegative patients Monitor with weekly CMV PCR during therapy for up to 2 months Pre-emptive ganciclovir if: Positive PCR and symptomatic (definite) Rising viral load and asymptomatic (consider) Fever of unknown origin and PCR unavailable	IV ganciclovir (5 mg/kg BD treatment dose, 5 mg/kg/d for prophylaxis, adjusted for renal function) Oral ganciclovir (1 g TDS prophylaxis) Valganciclovir (900 mg BD treatment, 900 mg/d prophylaxis, adjusted for renal function)	Pre-emptive treatment for at least 1 week (Keating *et al*, 2004) (Treat for 14–21 d if CMV disease)
Herpes viruses (VZV, HSV)		Famciclovir (500 mg BD) OR valacyclovir (500 mg daily or BD) OR acyclovir (200 mg TDS)	Up to 6 months after therapy
Hepatitis B	Screen prior to therapy for hepatitis B surface antigen and core antibody	Lamivudine (100 mg/d) commenced 4 weeks before and throughout chemotherapy	Continue through immune reconstitution (at least 6 months; Lau *et al*, 2003)
Fungal			
Fungi	Screen for colonisation prior to therapy (sputum culture/nasal swab) CT of chest or sinuses if past history of invasive fungal infection or colonisation Consider prophylaxis for high-risk patient groups	Itraconazole cyclodextrin solution (2·5 mg/kg BD) preferred as provides some mould protection†. Monitor serum level	Up to 6 months after therapy
Pneumocystis jirovecii (formerly *P. carinii*)	Monitor CD4 count recovery	Trimethoprim-sulphamethoxazole, DS (BD twice weekly) Alternatives: Oral dapsone (100 mg 5 d a week) Nebulised pentamidine (300 mg monthly) Oral atovaquone (750 mg BD)	Minimum 6–12 months after therapy, or until CD4 counts exceed $0{\cdot}25 \times 10^9$ cells/l
Tropical/endemic			
Strongyloides stercoralis	Baseline serology, stool specimens and eosinophil count if from endemic region. Treat prior to therapy if positive Endemic regions include: SE Asia, Mediterranean and Northern Australian indigenous populations (Davis *et al*, 2003)	Ivermectin (200 μg/kg) single dose	Single dose

Table II. (*Continued*)

Infection	Surveillance strategy	Drug treatment or prophylaxis (dose)	Duration*
Latent tuberculosis	Baseline screening of patients from endemic areas: Tuberculin skin test prior to therapy‡ Treatment if tuberculin test positive (≥5 mm) and active TB excluded. High-risk areas: Africa, Southeast Asia, Western Pacific, Eastern Mediterranean, Indigenous groups (ATS guidelines, 2000)	Isoniazid (300 mg/d)	12 months
Other infections to consider are endemic moulds (histoplasmosis, coccidiomycoses and blastomycosis), scabies (Davis *et al*, 2003), melioidosis (Davis *et al*, 2003)			

*Duration of prophylaxis should take into account the stage of disease, number of prior therapies, response to alemtuzumab therapy and CD4 count recovery.
†Voriconazole use associated with emergence of resistant fungi and should be used with caution.
‡The use of Quantiferon testing has not been evaluated in the immunocompromised patient and should be used with caution.

malignancies, one study described the risk of CMV pneumonia after alemtuzumab as 0·6% (Nosari *et al*, 2004). The use of filgrastam to reduce the severity of early neutropenia was associated with increased risk of CMV reactivation (Gibbs *et al*, 2005; Lin *et al*, 2005).

Laurenti *et al* (2004) described the use of oral ganciclovir 1000 mg t.d.s. to successfully suppress CMV DNAaemia in eight patients with previously treated CLL receiving alemtuzumab. The median time to suppression after commencing ganciclovir and withholding alemtuzumab was 14 d. Once virological suppression was achieved, ganciclovir was ceased and oral acyclovir 800 mg t.d.s. was recommenced. There was no recurrence of viraemia during the subsequent follow-up (median of 8 months), although the number of patients followed was small. There was no CMV disease encountered, nor toxicity from oral ganciclovir; in particular, there was no neutropenia, suggesting that this approach may be useful in the outpatient setting. Because of the low toxicity of preemptive therapy with ganciclovir and oral valganciclovir in response to the detection of CMV DNAaemia, it is unlikely that natural history of untreated CMV reactivation including risk factors for progression to CMV disease will be evaluated in a large cohort of patients.

There is a definite role for routine screening for CMV reactivation in all seropositive patients receiving alemtuzumab, although the interpretation of positive PCR remains problematic in this population. The PCR approach to surveillance has the advantage that white cells are not required (unlike the antigenaemia test) and neutropenia is a recognised complication of alemtuzumab. Both the British (Oscier *et al*, 2004) and North American guidelines (National Cancer Institute, 2005) recommend routine surveillance. We support the recommendations of Keating *et al* (2004) for a short course of ganciclovir for symptomatic patients with a positive CMV PCR test. The approach to the asymptomatic patient with rising CMV viral load is less clear. The appropriate duration of therapy is unknown, but monitoring CMV viral load may be helpful to determine the response to therapy. The UK guidelines also recommend the use of irradiated blood products (Oscier *et al*, 2004).

A variety of other viruses recognised to be associated with defects of CMI, including adenovirus (Cavalli-Bjorkman *et al*, 2002) and molluscum contagiosum (Pitini *et al*, 2003), have caused severe or disseminated infection. Epstein–Barr virus (EBV)-related disease (haemo-phagocytosis, large-cell lymphoma; Abruzzo *et al*, 2002; O'Brien *et al*, 2003; Enblad *et al*, 2004) has been reported in both CLL and patients with peripheral T-cell non-Hodgkin lymphoma, where EBV is commonly associated with the underlying disease. The possibility of infection with other viruses, such as human herpes virus 6 and parvovirus should be considered in patients with unusual haematological side effects, such as pancytopenia or aplastic anaemia (Herbert *et al*, 2003).

Finally, although there is little data, we predict that alemtuzumab may impact on other chronic viral infections,

such as hepatitis B. This is likely to be significant with increasing use of this agent outside of trial patients and in populations where the prevalence of the hepatitis B carrier state or chronic infection is high. Reactivation of hepatitis B virus (HBV) in hepatitis B surface antigen (HbsAg)-positive patients is a well-documented complication of cytotoxic or immunosuppressive therapy and has also been observed after treatment with rituximab, which also depletes B-cells (Heider *et al*, 2004; Tsutsumi *et al*, 2004). Lamivudine has been used effectively to prevent reactivation in this setting but should be continued through the period of immune reconstitution as this is the period of highest risk for a flare of hepatitis B. Further, patients with viral persistence after natural infection with a positive hepatitis B core antibody (HBc) and negative HbsAg have been identified as at risk. Two cases of HBV reactivation with alemtuzumab have recently been reported (Iannitto *et al*, 2005). The first case had seroreversion from anti-HBs to HbsAg-positive after 4 weeks of alemtuzumab therapy. The second case was HBsAg and HBV-DNA seronegative and anti-HBs and anti-HBc positive before treatment. Although lamivudine prophylaxis was continued up to 3 months after alemtuzumab, clinical and laboratory features of acute hepatitis B developed 2 months after the cessation of lamivudine. These cases illustrate the possibility of infection reactivating despite presence of hepatitis B antibody and absence of HBsAg at baseline and the potential benefit of continuing lamivudine until after immune reconstitution. We recommend hepatitis serology screening to include HBc (Lau *et al*, 2003) and continuation of lamivudine for at least 6 months after cessation of alemtuzumab. Monitoring of CD4 cell recovery may be useful in this group of patients. Chronic hepatitis B and C have both been shown to progress more rapidly in patients with profound defects of CMI, such as in human immunodeficiency virus (HIV) infection or after solid organ transplant. Screening for hepatitis infection should be mandatory prior to alemtuzumab therapy.

Bacterial/mycobacterial infections

Bacterial infections including septicaemia, meningitis and pneumonia occur early during treatment with alemtuzumab (<8 weeks) and accounted for over a third of infectious complications in the CLL and CTCL cohorts.

Disseminated mycobacterial infection and tuberculosis (TB) pneumonia have occurred late after treatment (one death after 10 months) (Lundin *et al*, 2003), and *Mycobacterium bovis* (Abad *et al*, 2003) and *Mycobacterium xenopi* (Weinblatt *et al*, 1995) infections have also been reported. Targeting testing for latent TB, including chest X-ray and tuberculin skin test, should be considered prior to onset of therapy in patients from endemic areas or individuals with a history of exposure. Immunosuppressive therapy or the underlying disease may affect interpretation of the tuberculin test. Similar to other immunosuppressed patients a tuberculin skin test result of ≥5 mm should be considered positive (American Thoracic Society, 2000). The performance of the QuantiFERON®-TB Test using recombinant ESAT-6 and CFP-10 is not well evaluated in immunosuppressed patients and is not currently recommended (Mazurek & Villarino, 2003).

Trimethoprim-sulphamethoxazole given for *Pneumocystis jiroveccii* prophylaxis may also offer some protection against bacterial pathogens, such as *Nocardia*, *Listeria* and *Burkholderia pseudomallei* (Avery & Ljungman, 2001).

Fungal infections

Of greater concern is the range of invasive fungal infections (IFI) that have been observed, particularly in the pretreated groups for both CLL and peripheral T-cell lymphoma (PTCL), and which have been responsible for several infection-related deaths. Only one study (Lundin *et al*, 2004) used fluconazole as antifungal prophylaxis. Systemic candidiasis is relatively uncommon, accounting for 4/33 (12·1%) of reported fungal infections. Perhaps candidiasis is less common than mould infections as alemtuzumab does not impact on the functional integrity of the intestinal epithelium (and cause mucositis), or rarely causes profound neutropenia, both significant factors for the development of invasive candidiasis in patients with haematological malignancies (Marr & Walsh, 2003). Therefore, the risk of invasive candidiasis should be assessed on an individual patient basis taking into account these and other recognised risk factors, such as renal impairment, broad-spectrum antibiotic therapy, and the presence of indwelling catheters (Wey *et al*, 1989).

Mould infections account for 17–20% of infections. *Zygomycetes*, *Fusarium*, *Scedosporium*, *Aspergillus* and *Cryptococcus* have all been reported. In our experience (Gibbs *et al*, 2004) 7 of 10 patients with CTCL who received alemtuzumab had a proven IFI, with moulds accounting for five of seven infections, although antifungal prophylaxis with either fluconazole or an *Aspergillus*-directed azole has been routine practice at our institution. Indeed, given the broad spectrum of fungal infections seen, the use of a broader spectrum azole for all heavily pretreated patients warrants further investigation. Emerging reports of breakthrough mould infections with zygomycoses in stem cell transplant recipients receiving voriconazole prophylaxis are a cause for concern (Imhof *et al*, 2004; Kontoyiannis *et al*, 2005). This trend has not been apparent with itraconazole prophylaxis (Prentice *et al*, 2000; Wingard, 2005). Although the majority of fungal infections occur within 3 months of alemtuzumab therapy, late infections have been reported and prophylaxis, if used may need to be prolonged for 6 months. An alternative approach might be to adopt a low threshold for investigation for IFI with imaging of chest or sinuses during the highest risk period, and pretreatment screening for colonisation. The utility of newer tests for early diagnosis of IFI, such as *Aspergillus galactomannan* and pan-fungal PCR, should also be explored. At present, antifungal prophylaxis with a broad-spectrum azole, such as itraconazole, may be warranted but voriconazole should be used with caution.

Endemic or tropical infections

There are several important tropical or endemic infections that are seen more frequently in the immunosuppressed patient and that should be considered prior to commencing alemtuzumab. In some, screening for latent infection is possible, in others a heightened clinical suspicion is required in the setting of infection.

Impaired CMI is the major risk factor for reactivation of endemic mycoses, namely histoplasmosis, blastomycoses and coccidiomycoses. While uncommon in cancer patients, life-threatening disseminated infection can occur. Endemic areas include southern Arizona, central California, southern New Mexico, and west Texas. Serological tests for histoplasmosis and coccidiomycoses may not be positive in the immunosuppressed patient and should not be performed. Diagnosis requires the use of histopathology/culture or antigen tests (Chandrasekar, 2003). Comprehensive practice guidelines for the management of patients with these endemic mycoses (Galgiani *et al*, 2000; Chapman *et al*, 2000; Wheat *et al*, 2000) are available on the Infectious Disease Society of America website (IDSA, 2005).

The risk of opportunistic parasitic and protozoal infections, such as malaria, *Strongyloides*, and toxoplasmosis, in patients treated with alemtuzumab is unknown. There is a theoretical risk of these infections in the setting of impaired CMI. *Toxoplasma gondii* infection is very rare in the setting of haematological malignancies (Pagano *et al*, 2004). Trimethoprim-sulphamethoxazole prophylaxis has some activity against *Toxoplasma* but does not completely protect against reactivation (Slavin *et al*, 1994). *S. stercoralis* hyperinfection syndrome (pulmonary infiltrates, fever, abdominal pain or septic shock) has been reported in immunosuppressed patients receiving steroids and cyclophosphamide (de Silva *et al*, 2002). Screening with serology, stool microscopy and eosinophil count should be performed in all patients identified as potentially at risk depending on the country of origin. This would include Southeast Asia, Mediterranean and Northern Australian indigenous populations (de Silva *et al*, 2002). The sensitivity of current diagnostic methods is not sufficiently high enough to exclude chronic infestation in a patient about to begin immunosuppression.

Other infections localised to certain geographic areas may also be important to consider. Melioidosis is a bacterial infection caused by *Burkholderia pseudomallei* in tropical areas of Northern Australia and Southeast Asia. Serology should be performed prior to immunosuppression and swabs performed if these are positive (Davis *et al*, 2003).

Monitoring lymphocyte recovery

The relationship between CD4 lymphocyte depletion and the risk of opportunistic infections has been extensively studied in HIV infection (Masur *et al*, 1989), and monitoring CD4 counts and CD4/CD8 ratios are routinely performed (Kaplan *et al*, 2002). This relationship is not well described in the oncology population, although several studies suggest that there is indeed increased risk for viral and *P. jirovecii* pneumonia infections with low CD4 counts (Anaissie *et al*, 1998; Mansharamani *et al*, 2000; Hughes *et al*, 2005). The pattern of cellular reconstitution after alemtuzumab has been described earlier. Lundin *et al* (2004) demonstrated that CD4 counts are usually $<0{\cdot}05 \times 10^9$/l at the end of treatment and only start to rise after 9 months. However, these patients received alemtuzumab as first line therapy, and infectious complications were uncommon. Both alkylating agents and purine analogues cause profound lymphocyte depletion in both malignant and normal lymphocyte populations, and prior treatment with these agents will increase the degree of immune suppression (Mackall, 2000). Moreover, an increasing CD4 cell count may not represent a functioning T-cell system, as T-cell receptor diversity is restricted, limiting polyclonal expansion that may persist for many months (Mackall, 2000). The recovery of CD4 counts is also slower with increasing age because of the reliance on relatively inefficient thymic independent pathways (Mackall, 2000).

For the treatment of patients with CLL, Keating *et al* (2004) recommended continuation of anti-infective prophylaxis until CD4 counts reach 0·25 × 109 cells/l. The product information for alemtuzumab recommends continuing for 2 months or until counts achieve $0{\cdot}2 \times 10^9$ cells/l whichever comes first. This approach probably comes from the controlled studies in HIV that have demonstrated significant infection risk for *P. jirovecii* pneumonia with peripheral cell counts of $<0{\cdot}2 \times 10^9$ cells/l.

One approach would be to measure baseline CD4 counts at the end of treatment and then again at 9 months and 3-monthly thereafter until counts exceed $0{\cdot}25 \times 10^9$ cells/l, although it should be emphasised that immune system alterations in cancer and associated therapies are complex, and the role of monitoring lymphocyte subsets is uncertain.

Conclusions

Knowledge of the range of infections and increased risks in patients undergoing alemtuzumab treatment (particularly those who have been heavily pretreated or who have advanced disease) enables a targeted approach to surveillance and infection prophylaxis.

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