Original Article

Infectious Complications Associated With Immunomodulating Monoclonal Antibodies Used in the Treatment of Hematologic Malignancy

Sophia Koo, MD,[a] and Lindsey R. Baden, MD,[a,b] *Boston, Massachusetts*

Key Words
Monoclonal antibodies, infectious complications

Abstract
Immunomodulating monoclonal antibodies are a relatively new addition to the armamentarium of cancer therapeutics and have been shown to improve clinical outcomes in patients with various hematologic malignancies. Because of their targeted nature, these agents are often believed to be less immunosuppressive than standard cytotoxic chemotherapeutic agents. A clear causal association between an immunomodulating therapy and its infectious sequelae is often difficult to discern because of the burden of comorbid illness, intrinsic immunosuppression from the underlying malignancy, use in the salvage setting, and prior and concomitant use of immunosuppressive agents in this patient population. This article evaluates better-established and anecdotal infectious complications associated with major immunomodulating therapies used in hematologic malignancy and hematopoietic stem cell transplantation, including rituximab, alemtuzumab, gemtuzumab ozogamicin, infliximab, dacluzimab, and basiliximab. (*JNCCN* 2008;6:202–213)

Monoclonal antibodies to various specific cellular targets have become widely used over the past several years

From [a]Brigham & Women's Hospital and Harvard Medical School and [b]Dana-Farber Cancer Institute, Boston, Massachusetts.

Submitted October 15, 2007; accepted for publication December 21, 2007.

The authors have no financial interest, arrangement, or affiliation with the manufacturers of any products discussed in the article or their competitors.

Correspondence: Sophia Koo, MD, Division of Infectious Diseases, Brigham & Women's Hospital, 15 Francis Street, PBB-A4, Boston, MA 02115. E-mail: skoo@partners.org

Medscape: Continuing Medical Education online

Medscape, LLC is pleased to provide online continuing medical education (CME) for this journal article, allowing clinicians the opportunity to earn CME credit. Medscape, LLC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide CME for physicians. Medscape, LLC designates this educational activity for a maximum of 1.0 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity. All other clinicians completing this activity will be issued a certificate of participation. To participate in this journal CME activity: (1) review the learning objectives and author disclosures; (2) study the education content; (3) take the post-test and/or complete the evaluation at www.medscape.com; (4) view/print certificate.

Learning Objectives

Upon completion of this activity, participants will be able to:

- Describe the actions of rituximab when used for hematologic malignancy
- Identify the US Food and Drug Administration (FDA)-approved indication for alemtuzumab for hematologic malignancy
- List infectious complications associated with use of alemtuzumab
- List major toxicities of gemtuzumab
- Describe the incidence of serious infections in patients using infliximab and adalimumab

because of their impressive efficacy in treating many hematologic malignancies. Although traditional systemic cytotoxic chemotherapies lead to nonselective immunosuppression and significant infectious complications, monoclonal antibodies should theoretically cause fewer infectious sequelae because of their highly targeted nature. This article describes the specific infections associated with each major immunomodulating monoclonal antibody used to treat hematologic malignancies (Table 1).

Rituximab

Rituximab is a chimeric murine–human monoclonal antibody that targets the CD20 surface antigen expressed in high levels by most normal and malignant B lymphocytes. It has been shown to improve clinical outcomes of patients with $CD20^+$ B-cell non–Hodgkin's lymphoma (NHL), and has been used successfully to treat patients with chronic lymphocytic leukemia (CLL), HIV-associated NHL, and post-transplant lymphoproliferative disorder (PTLD).

Rituximab induces cell lysis through various mechanisms, including complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and direct signaling of apoptosis. It is known to cause a sustained depletion of peripheral blood B lymphocytes soon after infusion, with recovery of normal B-cell populations after 6 to 9 months. Despite this depletion, rituximab has not been clearly shown to cause a significant decrease in circulating immunoglobulin levels, although it has been linked to an impaired secondary humoral response to recall antigens.[1] Because of its specificity for CD20, rituximab is not known to affect T-cell populations or cell-mediated immunity.

In multiple randomized controlled trials of standard chemotherapy regimens with or without rituximab for treating NHL, addition of rituximab was shown to significantly improve clinical outcomes with no detectable increase in infectious complications.[2] In certain studies of patients with HIV-associated NHL, addition of rituximab to standard chemotherapy regimens was associated with increased infectious complications, particularly in patients with CD4 cell counts of less than 50 cells/μL. In pooled results from 3 phase II trials of patients with HIV-associated B-cell NHL receiving rituximab in combination with cyclophosphamide, doxorubicin, and etoposide (CDE), 31% of patients developed grade III to IV infectious complications, compared with 20% incidence reported in prior studies of CDE alone in patients with HIV-negative NHL and poor prognosis. The median CD4 count in this population was 161 cells/μL (range, 3–691). Despite prophylaxis with trimethoprim-sulfamethoxazole and fluconazole, 10 (14%) developed serious opportunistic infections within 3 months of finishing chemotherapy, including 3 cases of cytomegalovirus (CMV) retinitis, 3 cryptosporidiosis, 2 pulmonary tuberculosis, 1 *Pneumocystis jirovecii* pneumonia (PCP), and 1 salmonellosis.[3] In a phase III trial of 150 patients with untreated $CD20^+$ HIV-associated NHL randomized to treatment with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP with rituximab (R-CHOP), a statistically significant difference was seen in infectious mortality: 14% in patients receiving R-CHOP and 2% in patients receiving CHOP ($P = .035$). Most infections were not opportunistic, and only 1 death was attributed to a fungal pneumonia; 60% of infectious deaths occurred in patients with CD4 counts less than 50 cells/μL.[4]

A more recent phase II study of 61 patients with HIV-associated NHL treated with R-CHOP used more stringent exclusion criteria, excluding patients with CD4 counts less than 100 cells/μL, prior opportunistic infections, or poor performance status, and reported a low rate of infectious complications, with 1 death from septic shock and another from HIV encephalopathy.[5] Immunoglobulin levels were not measured in these studies, but a single case report describes a patient with HIV-associated NHL who developed persistent hypogammaglobulinemia after receiving R-CHOP.[6] The additive immunosuppression from HIV-associated T-lymphocyte deficits and hypogammaglobulinemia may predispose this subpopulation of patients to more severe infections.

Rituximab has been used to treat B-cell CLL in several single-arm studies, often in combination with fludarabine. A retrospective comparison of patients in 2 trials of first-line therapy of B-cell CLL—the first with fludarabine and rituximab and the second with fludarabine alone—showed a significantly higher response rate in the rituxan group, without an appreciable difference in the rates of grade III to IV infection or herpesvirus reactivation.[7]

Several viral infections have been reported in association with rituximab. Humoral immunity and neu-

Table 1 Established and Anecdotal Infectious Complications Associated with Monoclonal Antibodies Used in the Treatment of Hematologic Malignancy

Monoclonal Antibody	Target	Year of FDA Approval	FDA-Approved Indications	Relevant Off-label Uses	Established Infectious Complications	Anecdotal Infectious Complications
Rituximab	CD20	1997	• Relapsed or refractory low-grade or follicular CD20+ B-cell NHL • First line treatment of diffuse large B-cell, CD20+ NHL in combination with CHOP or other anthracycline-based chemotherapy regimens • First-line treatment of follicular CD20+ B-cell NHL in combination with CVP chemotherapy • Low-grade CD20+ B-cell NHL in patients with stable disease or partial or complete response after first-line CVP chemotherapy • In combination with methotrexate, adults with moderate to severe rheumatoid arthritis with an inadequate response to anti–TNF-α therapies	• CLL • HIV-associated NHL • Waldenström's macroglobulinemia • ITP • Cryoglobulinemia	• Hepatitis B reactivation	• Enteroviral meningoencephalitis • Relapsing *Babesia microti* infection • PML • CMV • VZV • Parvovirus B19 • West Nile virus
Alemtuzumab	CD52	2001	• B-cell CLL previously treated with alkylating agents, inadequate response to fludarabine therapy	• First-line therapy of CLL • NHL	• CMV • IFI • PCP	• Adenovirus • Other respiratory viruses (PIV-3, RSV) • HHV-6 • PML • Parvovirus B19 • Polyoma viruria
Gemtuzumab	CD33	2000	• CD33+ AML in first relapse for patients ≥ 60 years, not candidates for cytotoxic chemotherapy		• Bacteria • HSV	
Infliximab	TNF-α	1998	• Crohn's disease • Ulcerative colitis (infliximab) • Rheumatoid arthritis	• Steroid-resistant acute GVHD	• Tuberculosis • Endemic fungi (histoplasmosis, cryptococcosis, coccidioidomycosis) • IFI • Sepsis	• PCP • Listeriosis • Nocardiosis • VZV
Etanercept	TNF-α	1999	• Juvenile rheumatoid arthritis (etanercept) • Plaque psoriasis • Psoriatic arthritis			
Adalimumab	TNF-α	2002	• Ankylosing spondylitis			
Daclizumab	IL-2R/ CD25	1997	• Prophylaxis of acute renal allograft rejection	• Steroid-resistant acute GVHD	• CMV	• Toxoplasmosis • EBV-associated PTLD
Basiliximab	IL-2R/ CD25	1998				

Abbreviations: AML, acute myelogenous leukemia; CHOP, cyclophosphamide doxorubicin vincristine prednisone; CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; CVP, cyclophosphamide vincristine prednisone; EBV, Epstein-Barr virus; FDA, U.S. Food and Drug Administration; GVHD, graft-versus-host disease; HHV-6, human herpesvirus-6; HSV, herpes simplex virus; IFI, invasive fungal infection; IL, interleukin; ITP, idiopathic thrombocytopenic purpura; NHL, non–Hodgkin's lymphoma; PCP, Pneumocystis jirovecii pneumonia; PIV-3, parainfluenza virus-3; PML, progressive multifocal leukoencephalopathy; PTLD, post-transplant lymphoproliferative disorder; RSV, respiratory syncytial virus; TNF, tumor necrosis factor; VZV, varicella zoster virus.

tralizing antibodies are believed to play an important role in the containment of latent hepatitis B virus (HBV) infection. Multiple reports describe reactivation of latent HBV after rituximab therapy, especially in patients with HBV surface antigen positivity before chemotherapy, but also in those with isolated HBV core antibody positivity.[8] Fulminant hepatic failure from HBV reactivation has been reported as late as 1 year after rituximab therapy.[9] HBV surface antibody titers have been shown to diminish or even disappear soon after rituximab administration in some patients.[10,11] Some reports have shown that patients receiving lamivudine prophylaxis during rituximab-containing chemotherapy regimens experienced no reactivation of their latent HBV infection.[11,12] However, escape mutants have developed after rituximab therapy,[13] including a tyrosine-methionine-aspartate-aspartate (YMDD) mutant strain that developed during lamivudine monotherapy,[14] which led to fulminant hepatic failure. Assessment of HBV serologic status is important before initiating rituximab therapy, as is regular surveillance for patients at risk for HBV reactivation. Optimal treatment strategy (prophylactic, preemptive, or early) and regimen are not well-defined.

Humoral immunity is known to play an important role in the containment of enteroviral infections. In pediatric patients, X-linked agammaglobulinemia has been associated with development of chronic enteroviral meningoencephalitis. Serious enteroviral infections have been described after rituximab therapy, including a patient with diffuse large B-cell NHL who developed enteroviral encephalitis 7 months after treatment with R-CHOP. The patient had a mild immunoglobulin G hypogammaglobulinemia and his symptoms improved with intravenous immunoglobulin, but he died of intercurrent infection.[15] Two other cases of enteroviral meningoencephalitis were described in patients receiving rituximab, both with low immunoglobulin G levels, and an identical strain of echovirus 13 was isolated from successive cerebrospinal fluid samples in 1 of these patients.[16,17]

Papovavirus infections have been linked to rituximab therapy in rare case reports, although a causal relationship remains uncertain. In patients undergoing autologous hematopoietic stem cell transplantation (HSCT), 2 cases of JC virus infection were reported at 9 and 20 months after transplantation,[18] soon after peritransplant rituximab was added to an HSCT protocol. Both patients had relative CD4 lymphopenia and previously underwent other immunosuppressive therapy. BK virus–associated leukoencephalopathy developed in a single patient soon after receiving rituximab, although this patient also had a complicated history of prior treatment for Hodgkin disease.[19]

Scattered reports exist of herpesvirus reactivation and infection (CMV and herpes zoster) in patients receiving rituximab, often in combination with other cytotoxic chemotherapies.[18,20–22] Rituximab is also associated with an inability to clear *Babesia microti* infection. In a case-control study of patients with persistent babesiosis after a standard course of antimicrobial therapy, 8 of 14 subjects had previously received rituximab-containing chemotherapy regimens, including 3 patients who ultimately died of it.[23] Parvovirus B19 with pure red cell aplasia[24–26] and West Nile virus[27,28] have also been linked to rituximab in case reports.

Much heterogeneity exists in rituximab dosing regimens for many indications, and whether higher or more frequent dosing strategies carry a greater infectious risk is unclear from available evidence.

Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody directed against CD52, a surface antigen expressed in high levels by B-cell CLL and T-prolymphocytic leukemia cells, along with normal B and T lymphocytes, monocytes, macrophages, and NK cells. Alemtuzumab has been shown to destroy target cells through antibody-dependent cellular cytotoxicity, complement-mediated cytolysis, and induction of apoptosis, with profound lympholysis and severe sustained immunosuppression. CD4 and -8 T-cell counts nadir approximately 4 weeks after alemtuzumab, and median counts remain at less than 25% of their baseline values until approximately 9 months postchemotherapy.[29] Alemtuzumab improves outcomes in first-line and salvage therapy of CLL, T-cell prolymphocytic leukemia, and NHL; as a component of reduced-intensity HSCT conditioning; as induction immunotherapy in solid organ transplantation; and in the treatment and prophylaxis of graft-versus-host disease (GVHD) in allogeneic HSCT recipients, but has been associated with a wide spectrum of major infectious complications.

High rates of standard and opportunistic infections and extremely delayed recovery of functional immune status have been reported with alemtuzumab

use in salvage therapy of refractory or relapsed CLL. In a phase II study of alemtuzumab in 24 patients with fludarabine-refractory disease, opportunistic infections, including PCP, invasive aspergillosis (IA), candidiasis, disseminated varicella-zoster virus (VZV), mycobacterial infection, and CMV, developed in 10 patients (41.7%). Opportunistic infections were more common in patients whose CLL did not respond to alemtuzumab therapy than in those whose did. Patients were shown to have profound CD4 and -8 depletion, with nadir counts 4 weeks into therapy.[30] Another phase II study of alemtuzumab in 29 patients with relapsed or refractory CLL also showed a high rate of nonopportunistic and opportunistic infections, with 2 cases of PCP, 4 bacterial pneumonias, 11 (38%) localized herpes simplex virus (HSV) reactivations, and 4 cases of sepsis.[31] Notably, these studies preceded the routine use of PCP and herpesvirus prophylaxis in patients receiving alemtuzumab.

A larger multicenter study investigating the benefit of alemtuzumab in patients with refractory or relapsed B-cell CLL previously exposed to alkylating agents in whom treatment with fludarabine failed, and who received mandatory PCP and herpesvirus prophylaxis, showed lower overall rates of grade III to IV infection (26.9%) and opportunistic infection.[32] Among these patients, 10% developed sepsis, 8% experienced CMV reactivation, and 6% experienced HSV reactivation. Severe infections were less frequent in patients whose CLL responded to alemtuzumab therapy. Only 7 patients developed opportunistic infections during the study or within 30 days of alemtuzumab administration (including 1 PCP, 1 IA, 1 rhinocerebral mucormycosis, 1 invasive candidosis, and 1 cryptococcal pneumonia). After 30 days, 4 patients developed VZV, 1 developed IA, and 1 developed *Listeria* meningitis. Over the entire follow-up period, 11 infectious deaths occurred. Patients were shown to have a profound decline in their CD4 and -8 populations to less than 0.01% of their baseline values, with a nadir 4 weeks after alemtuzumab treatment. Similar rates of nonopportunistic and opportunistic infections, with a relatively high incidence of CMV reactivation and invasive fungal infections (IFI), have been described in other studies of alemtuzumab in patients with refractory CLL.[33,34]

A retrospective evaluation of 27 patients receiving alemtuzumab for lymphoproliferative disorders at the authors' institution (21 with CLL) also showed a high rate of infectious complications, including 12 opportunistic infections in 9 patients (33%) and 30 nonopportunistic infections in 22 patients (82%).[35] All patients were heavily pretreated with a median of 4 prior chemotherapy regimens, and all received PCP and herpesvirus prophylaxis. The spectrum of opportunistic infections was diverse, with 3 cases of IA, 2 of pyomyositis and bacteremia, 1 of disseminated histoplasmosis, 1 of adenovirus pneumonia, 1 of progressive multifocal leukoencephalopathy (PML), 1 of cerebral toxoplasmosis, 1 of disseminated acanthamebiasis, and 1 of CMV pneumonitis and colitis. The median time to development of opportunistic infections after starting alemtuzumab was 169 days (range, 8–570). Of the nonopportunistic infections, many were viral upper respiratory infections, but 8 episodes of bacteremia or sepsis (including 3 cases of fatal enterococcal sepsis), 6 pneumonias, 4 cellulitis, and 1 *Clostridium difficile* colitis occurred. Twelve patients (44%) developed asymptomatic CMV reactivation and 7 of 10 deaths during the follow-up period were attributed to infection.

Other retrospective studies of patients with refractory lymphoproliferative disease treated with alemtuzumab have confirmed high rates of CMV reactivation. In one study, 15% of patients developed symptomatic CMV viremia a median of 28 days (range, 20–30) after alemtuzumab treatment, but underwent successful preemptive therapy with ganciclovir, without subsequent CMV disease. A trend was seen toward prior rituximab use as a risk factor for CMV viremia (relative risk, 5.3 [0.89–32; $P = .07$]).[36] Another study of patients with previously treated CLL receiving alemtuzumab showed a high proportion (66%) of asymptomatic CMV reactivation, although no patients progressed to CMV disease with preemptive valganciclovir therapy.[37]

A trial of patients with CLL in first remission randomized to consolidation therapy with alemtuzumab or placebo was closed prematurely because of a high rate of severe infections in the alemtuzumab arm. In the alemtuzumab group, 7 of 11 patients (64%) developed opportunistic infections, including IA, tuberculosis reactivation, and a wide range of herpesvirus infections (e.g., HSV, human herpesvirus 6, CMV, VZV) despite herpesvirus prophylaxis with famciclovir.[38]

Infectious rates did not differ significantly from those of alemtuzumab treatment alone in patients receiving alemtuzumab and rituximab for refractory or relapsed lymphoproliferative disorders; 52% of patients

developed an infection and 24% developed CMV antigenemia, of which 54% were symptomatic.[39] Alemtuzumab in conjunction with fludarabine is highly active in treating refractory CLL,[40] but their cumulative infectious toxicities have not been defined.

Alemtuzumab has also been used effectively in first-line therapy of CLL, with lower rates of CMV reactivation and opportunistic infection than in patients with refractory CLL, possibly because of a lack of exposure to other cytotoxic chemotherapies. Of 9 patients with progressive CLL receiving alemtuzumab as first-line therapy, 1 developed CMV reactivation and pneumonitis.[41] In a phase II study of alemtuzumab in first-line treatment of 41 patients with symptomatic CLL, 10% developed CMV reactivation and none developed CMV disease. One patient who was unable to receive PCP prophylaxis because of allergy developed PCP.[42]

Prolonged T-cell lymphopenia lasting up to 320 days after completion of therapy has been shown with alemtuzumab therapy in patients with refractory T-cell prolymphocytic leukemia, accompanied by the expected spectrum of infections: cryptococcal meningitis, fungal pneumonia, CMV reactivation, and VZV.[43] Infections, including opportunistic infections, seem to be less frequent in this population than in patients with underlying CLL.[44]

Alemtuzumab is effective in treating a subset of patients with refractory or relapsed NHL and is associated with a similar range of infectious complications, as in patients with CLL. In an early phase I/II study of 18 patients with relapsed NHL who did not receive routine PCP or herpesvirus prophylaxis, 1 patient developed PML and 1 PCP.[45] In a phase II study of 50 patients with relapsed or resistant low-grade NHL receiving alemtuzumab, those with peripheral T-cell lymphoma (PTCL) had the greatest response to therapy. Localized HSV infection developed in 22 patients (44%), 7 patients developed opportunistic infections (3 CMV pneumonitis, 2 IA, 1 tuberculosis, 1 PCP), 9 developed septicemia, and 7 developed non-PCP pneumonia.[46] Further studies of alemtuzumab in PTCL showed similar efficacy and infectious complications, with significant CMV reactivation, and several cases of IA and tuberculosis.[47,48] In a prospective multicenter study of 24 patients with PTCL treated with CHOP and alemtuzumab, a relatively low rate of CMV reactivation (9%) was seen, but several bacterial infections and opportunistic infections occurred despite itraconazole and herpesvirus prophylaxis and regular galactomannan antigen surveillance.[49]

Rates of CMV are high in studies of alemtuzumab for GVHD prophylaxis. In a comparison of patients enrolled in 2 prospective studies of HSCT for chronic lymphoproliferative disorders, a prophylactic regimen of fludarabine, melphalan, cyclosporine A, and alemtuzumab was associated with a higher incidence of CMV reactivation (85%) than cyclosporine and methotrexate (24%, $P < .001$), although patients had a markedly lower incidence of acute and chronic GVHD.[50]

Alemtuzumab reduces GVHD and graft rejection in conditioning regimens for nonmyeloablative allogeneic HSCT, but is also associated with high rates of CMV reactivation. At the authors' institution, a trend was seen toward more CMV infections in patients who received alemtuzumab undergoing HSCT (6 of 9 [66%]) than in matched patients undergoing HSCT who did not receive alemtuzumab (10 of 27 [37%]); $P = .15$).[35]

In patients with acute myelogenous leukemia (AML) and myelodysplastic syndromes (MDS) undergoing fludarabine, busulfan, and alemtuzumab conditioning for HSCT, a 59% cumulative 1-year CMV incidence occurred in recipient-seropositive, donor-seronegative patients. Within the 3 months before conditioning, 18% of patients had IA infections and received AmBisome therapy through the transplantation period, whereas the remainder received itraconazole prophylaxis, with only 1 case of IA during the study period. Of the 4 nonrelapse deaths, 1 was attributed to adenovirus, 1 to respiratory syncytial virus, and 1 to Epstein-Barr virus (EBV)–associated PTLD.[51] In another study of patients with AML and MDS receiving fludarabine, melphalan, and alemtuzumab conditioning for nonmyeloablative HSCT, 29% of patients developed CMV reactivation, with 1 case of CMV pneumonitis, and no patients developed IFIs.[52] In a study of 101 patients undergoing nonmyeloablative allogeneic HSCT with fludarabine, melphalan, and alemtuzumab conditioning, 51 (50%) patients developed CMV reactivation at a median of 27 days (range, 7–240); 92% of recipient-and donor-seropositive patients and 78% of recipient-seropositive, donor-seronegative patients developed CMV reactivation. CMV reactivation was more common in unrelated donor HSCT. Three patients (6% of patients at risk for CMV) developed definite CMV

disease (2 CMV pneumonitis and 1 enteritis) and 2 patients had possible CMV-related mortality; all 5 patients died despite monitoring and preemptive therapy. T-cell subset recovery was monitored regularly in 48 patients, and all experienced a recovery to 200 CD4 cells/μL at a median of 9 months.[53] Another study of patients receiving alemtuzumab as part of HSCT conditioning showed a 60% cumulative incidence of CMV infection at 1 year, with a median reactivation time of 24 days (range, 5–95), but only 1 patient developed CMV disease (colitis).[54]

Patients receiving alemtuzumab as part of HSCT conditioning have been shown to have an increased incidence and severity of adenovirus infections, with a higher frequency of adenovirus infection associated with lower absolute lymphocyte counts (ALC). Of patients receiving alemtuzumab in vivo, 40% developed probable or definite adenovirus disease and 2 patients died of fulminant hepatic adenovirus infection. Of 7 patients with an ALC less than 300/μL, 6 developed adenovirus disease compared with no patients with an ALC greater than this value. The median CD4 T-cell count was 30 cells/μL (range, 0–90) in 3 patients who developed adenovirus disease, and 155 cells/μL in patients who remained asymptomatic and cleared the virus.[55] In another study, 18.4% of patients undergoing conditioning with alemtuzumab developed adenovirus disease; 5 patients with adenovirus disease were unable to undergo tapering of their immunosuppression, and all died of progressive adenovirus disease within 6 weeks of onset of clinical symptoms. ALC at disease onset was significantly lower in patients who died (122 +/– 113 cells/μL) than in those who survived (447 +/– 393 cells/μL; $P = .01$).[56]

Alemtuzumab conditioning has also been associated with viral upper respiratory infections. In a retrospective assessment of 83 patients conditioned with fludarabine, melphalan, and alemtuzumab, 35 respiratory virus infections occurred in 25 patients (30.1%) at a median of 123 days (range, 1–561) from onset of therapy; 16 of these episodes (46%) were parainfluenza-3, 13 (37%) were respiratory syncytial virus, 5 (14%) were influenza A/B, and 1 was parainfluenza-1. Among these, 54% progressed to lower respiratory tract infection, but mortality was attributable to lower respiratory infection in only 2 patients.[57]

In one series, 11.6% of patients receiving alemtuzumab conditioning developed symptomatic human herpesvirus-6 encephalitis at a median of 60 days (range, 41–103), presenting with amnesia and seizures. All patients had received various immunosuppressants for acute GVHD. Patients received foscarnet with improvement, except for 1 patient who died of progressive encephalopathy and was found to have extensive bilateral loss of hippocampal neurons at autopsy.[58]

Other viral illnesses with reported associations with alemtuzumab include polyoma viruria,[59] HBV reactivation,[60] and pure red cell aplasia secondary to parvovirus B19 infection.[61,62]

When alemtuzumab is used, preventative strategies for herpesviruses, tuberculosis, and PCP should be established and a careful assessment performed of patient-specific infectious risk factors, such as prior infections or geographic exposures.

As with rituximab, a marked variability exists in alemtuzumab dosing regimens. Whether higher or more frequent dosing strategies carry a greater infectious risk is also not well defined by available data.

Gemtuzumab

Gemtuzumab ozogamicin (GO) is a humanized anti-CD33 antibody conjugated to calicheamicin, a potent antitumor antibiotic that cleaves double-stranded DNA at specific sequences. Approximately 90% of patients with AML have myeloid blast cells that express CD33 surface antigen, as do normal hematopoietic progenitor cells. The GO complex is internalized by target cells and the toxin is released intracellularly by hydrolysis. It has been shown to improve outcomes in patients aged 60 years or older with CD33+ AML in first relapse who are not candidates for cytotoxic chemotherapy. Major toxicities are prolonged myelosuppression and possibly an increase in veno-occlusive disease after HSCT; the spectrum of infectious complications is largely associated with the depth and duration of neutropenia.

In 3 pooled phase II studies of 142 patients with AML in first relapse undergoing GO monotherapy, 97% of patients developed grade III to IV neutropenia, with a mean time to absolute neutrophil count recovery to greater than 500/μL of approximately 40 days in patients with a clinical response to GO. Among 40 (28%) patients who developed grade III to IV infections, the most frequent were sepsis (16%) and pneumonia (7%).[63] In a report of 277 patients with $CD33^+$ AML in first recurrence treated with GO, 98% developed grade III to IV neutropenia, with

sepsis in 17% and pneumonia in 8%; 13 of 44 deaths within 28 days of GO administration were attributed to infection.[64]

Anti–Tumor Necrosis Factor Antibodies

Infliximab and adalimumab are monoclonal antibodies directed against tumor necrosis factor α (TNF-α). Infliximab, adalimumab, and a third anti–TNF-α agent, etanercept, which is a soluble TNF receptor, are effective therapies for multiple inflammatory conditions, including advanced Crohn's disease and rheumatoid arthritis. Infliximab and etanercept have also been used to treat steroid-refractory GVHD.

TNF-α plays a vital role in multiple aspects of cell-mediated immunity, including host resistance to intracellular infectious agents, formation of granulomas, differentiation of monocytes into macrophages, and recruitment of neutrophils and macrophages. Interference with TNF-α carries significant infectious risks, especially latent infections contained by an intact cell-mediated immune system, such as tuberculosis, nontuberculous mycobacteria, IA, candidiasis, endemic fungi, listeriosis, and nocardiosis.

The overall incidence of serious infections in patients receiving infliximab is 5.2 to 6.2 per 100 patient-years based on national registry data from the United Kingdom and Germany. The relative risk for tuberculosis has been estimated at 4.1 based on Swedish national registry data.[65] In patients with rheumatoid arthritis, a recent meta-analysis has shown an odds ratio of 2.0 (95% CI, 1.3–3.1) for serious infection and 3.3 (95% CI, 1.2–9.1) for malignancy in those receiving anti–TNF-α antibodies compared with those receiving placebo.[66] Of the 126 serious infections in this population, only 12 were granulomatous infections. In the FDA adverse event reporting system, granulomatous infections were more common in patients receiving infliximab (239/100,000) than etanercept (74/100,000).[67]

TNF-α has been implicated in the pathogenesis of acute GVHD after allogeneic HSCT, and infliximab and etanercept have been used successfully to abate the cytokine storm associated with steroid-refractory acute GVHD. This population is inherently at high risk for IFIs because of its loss of gastrointestinal barrier integrity and concomitant heavy immunosuppression, and the addition of potent immunomodulating therapy further increases this risk. In a series of 11 patients with acute steroid-refractory GVHD, only 2 with diarrhea from acute gastrointestinal GVHD experienced symptomatic improvement and survived. Two patients had IA before initiation of infliximab, and 6 of 11 patients (55%) died with an active IFI.[68] In a retrospective evaluation of 264 patients who underwent allogeneic HSCT, 53 (20%) developed grade III to IV GVHD. Of these, 11 (21%) were treated with infliximab, and 5 developed an IFI (including IA and zygomycosis) compared with 5 of 42 patients who were not treated with infliximab. No significant difference was seen in the cumulative steroid dose between the groups. In a Cox regression model, the adjusted hazard ratio of infliximab exposure for IFI was 13.6 (95% CI, 2.29–80.2; $P = .004$).[69] In a retrospective evaluation of 134 patients with steroid-refractory GVHD, 21 received infliximab therapy, of whom 10 (48%) developed 18 fungal infections, including 7 IA and 11 Candida infections. This study also described a total of 45 bacterial infections in 17 patients (81%) and 24 viral infections in 14 patients (67%), primarily CMV reactivation.[70] Etanercept, which is known to be a less-potent TNF-α inhibitor than infliximab, has also been studied in the treatment of steroid-refractory acute GVHD, with reported rates of CMV reactivation as high as 48%, fungal infection 19%, including IA and esophageal candidiasis, and 19% bacterial infection.[71] In a phase II study of steroid-resistant acute GVHD treated with dacluzimab and etanercept, 62% had CMV reactivation, and 52.3% died of infectious complications.[72]

Anti–Interleukin-2Rα Antibodies

Daclizumab and basiliximab are anti–interleukin (IL)-2Rα antibodies, which bind to the IL-2 receptor expressed on activated T lymphocytes, with competitive inhibition of IL-2 binding and abatement of IL-2–mediated lymphocyte proliferation, differentiation, and cytokine release. These antibodies eliminate antigen-specific alloreactive T cells, with blunting of the response to antigenic challenges, and are approved for prophylaxis of renal allograft rejection. Both have been used to treat steroid-refractory GVHD with significant infectious complications, comparable to other therapies for it.

Patients receiving daclizumab for steroid-refractory acute GVHD have high rates of infectious mortality, although the underlying disease and its prior therapies

carry an extremely high risk for infectious complications, and very little of the infectious risk may be attributable to daclizumab itself. The incidence of EBV-associated PTLD and toxoplasmosis seems higher than expected in this population. In one study of 43 patients with steroid-refractory GVHD, 3 developed EBV-associated PTLD during or after daclizumab treatment, all of which received a T-cell depleted HSCT from unrelated donors. Ten patients died of GVHD and infection and 7 of infection (not further defined).[73] In another small study, 14 of 16 patients who received daclizumab for steroid-refractory GVHD developed infectious complications, including 9 with CMV reactivation (4 CMV colitis), 1 toxoplasmosis, 12 sepsis, and 1 IA. Three infection-related deaths occurred during the study period.[74] In another study, daclizumab was associated with an 87% rate of CMV reactivation, a 42% rate of respiratory viral infections, including a fatal case of parainfluenza-3 infection, and 1 case of EBV-associated PTLD.[75] In a retrospective evaluation of 57 patients who received daclizumab for steroid-refractory acute GVHD, 54 (95%) patients developed an infection within 6 months of initiating daclizumab therapy, with high infection-associated mortality. Additionally, 50 (88%) had a bacterial infection, 29 (51%) had fungal infections, and 30 (53%) had viral infections; 35% developed CMV reactivation; 38 (67%) developed an IFI (7 IA, 19 candidiasis, 10 other yeast, 1 Scedosporium apiospermum, 1 Cunninghamella); and 4 developed EBV-associated PTLD. Other opportunistic infections of interest included 1 toxoplasmosis, 1 nocardia, 1 tuberculosis, 3 non–tuberculosis mycobacteria, 2 adenovirus, 4 respiratory syncytial virus, and 3 BK virus.[76]

Limited data on basiliximab for steroid-refractory acute GVHD show a comparable rate and range of infectious complications to daclizumab. In a retrospective evaluation of 34 patients, 19 infectious deaths occurred, 8 from bacterial sepsis, 4 from CMV and 6 IFI.[77] In a prospective phase II study of basiliximab for steroid-refractory acute GVHD, 15 of 23 (65%) patients developed infections, 10 of which were bacterial, with 4 deaths from sepsis; 5 experienced CMV reactivation, 2 developed IFI, and 1 developed cerebral toxoplasmosis.[78]

Conclusions

The emergence of targeted immunotherapies has allowed experts to perform immunologic surgery and extend potentially lifesaving therapies to patients. The immunologic consequences are salutary for the underlying disease process but may expose patients to novel primary infections and reactivations of latent infections. Defining the infectious complications associated with different targeted immunotherapies may provide a better understanding of the host defenses required to control certain pathogens and develop more effective prophylactic and monitoring strategies.

References

1. van der Kolk LE, Baars JW, Prins MH, et al. Rituximab treatment results in impaired secondary humoral immune responsiveness. Blood 2002;100:2257–2259.
2. Rafailidis PI, Kakisi OK, Vardakas K, et al. Infectious complications of monoclonal antibodies used in cancer therapy: a systematic review of the evidence from randomized controlled trials. Cancer 2007;109:2182–2189.
3. Spina M, Jaeger U, Sparano JA, et al. Rituximab plus infusional cyclophosphamide, doxorubicin, and etoposide in HIV-associated non-Hodgkin lymphoma: pooled results from 3 phase 2 trials. Blood 2005;105:1891–1897.
4. Kaplan LD, Lee JY, Ambinder RF, et al. Rituximab does not improve clinical outcome in a randomized phase 3 trial of CHOP with or without rituximab in patients with HIV-associated non-Hodgkin lymphoma: AIDS-Malignancies Consortium Trial 010. Blood 2005;106:1538–1543.
5. Boue F, Gabarre J, Gisselbrecht C, et al. Phase II trial of CHOP plus rituximab in patients with HIV-associated non-Hodgkin's lymphoma. J Clin Oncol 2006;24:4123–4128.
6. Miles SA, McGratten M. Persistent panhypogammaglobulinemia after CHOP-rituximab for HIV-related lymphoma. J Clin Oncol 2005;23:247–248.
7. Byrd JC, Rai K, Peterson BL, et al. Addition of rituximab to fludarabine may prolong progression-free survival and overall survival in patients with previously untreated chronic lymphocytic leukemia: an updated retrospective comparative analysis of CALGB 9712 and CALGB 9011. Blood 2005;105:49–53.
8. Niscola P, Del Principe MI, Maurillo L, et al. Fulminant B hepatitis in a surface antigen-negative patient with B-cell chronic lymphocytic leukaemia after rituximab therapy. Leukemia 2005;19:1840–1841.
9. Perceau G, Diris N, Estines O, et al. Late lethal hepatitis B virus reactivation after rituximab treatment of low-grade cutaneous B-cell lymphoma. Br J Dermatol 2006;155:1053–1056.
10. Dervite I, Hober D, Morel P. Acute hepatitis B in a patient with antibodies to hepatitis B surface antigen who was receiving rituximab. N Engl J Med 2001;344:68–69.
11. Tsutsumi Y, Tanaka J, Kawamura T, et al. Possible efficacy of lamivudine treatment to prevent hepatitis B virus reactivation due to rituximab therapy in a patient with non-Hodgkin's lymphoma. Ann Hematol 2004;83:58–60.
12. Hamaki T, Kami M, Kusumi E, et al. Prophylaxis of hepatitis B reactivation using lamivudine in a patient receiving rituximab. Am J Hematol 2001;68:292–294.

13. Westhoff TH, Jochimsen F, Schmittel A, et al. Fatal hepatitis B virus reactivation by an escape mutant following rituximab therapy. Blood 2003;102:1930.
14. Law JK, Ali JA, Harrigan PR, et al. Fatal postlymphoma chemotherapy hepatitis B reactivation secondary to the emergence of a YMDD mutant strain with lamivudine resistance in a noncirrhotic patient. Am J Hematol 2006;81:969–972.
15. Padate BP, Keidan J. Enteroviral meningoencephalitis in a patient with non-Hodgkin's lymphoma treated previously with rituximab. Clin Lab Haematol 2006;28:69–71.
16. Quartier P, Tournilhac O, Archimbaud C, et al. Enteroviral meningoencephalitis after anti-CD20 (rituximab) treatment. Clin Infect Dis 2003;36:e47–49.
17. Archimbaud C, Bailly JL, Chambon M, et al. Molecular evidence of persistent echovirus 13 meningoencephalitis in a patient with relapsed lymphoma after an outbreak of meningitis in 2000. J Clin Microbiol 2003;41:4605–4610.
18. Goldberg SL, Pecora AL, Alter RS, et al. Unusual viral infections (progressive multifocal leukoencephalopathy and cytomegalovirus disease) after high-dose chemotherapy with autologous blood stem cell rescue and peritransplantation rituximab. Blood 2002;99:1486–1488.
19. Matteucci P, Magni M, Di Nicola M, et al. Leukoencephalopathy and papovavirus infection after treatment with chemotherapy and anti-CD20 monoclonal antibody. Blood 2002;100:1104–1105.
20. Aksoy S, Harputluoglu H, Kilickap S, et al. Rituximab-related viral infections in lymphoma patients. Leuk Lymphoma 2007;48:1307–1312.
21. Suzan F, Ammor M, Ribrag V. Fatal reactivation of cytomegalovirus infection after use of rituximab for a post-transplantation lymphoproliferative disorder. N Engl J Med 2001;345:1000.
22. Vallet S, Tempescul A, Tran A, et al. Cytomegalovirus-associated meningoradiculoneuritis after treatment of mantle cell lymphoma with a combination of chemotherapy and rituximab. Ann Hematol 2005;84:545–547.
23. Krause PJ, Gewurz BE, Hill D, et al. Persistent and relapsing babesiosis in immunocompromised patients. Clin Infect Dis 2008;46:370–376.
24. Sharma VR, Fleming DR, Slone SP. Pure red cell aplasia due to parvovirus B19 in a patient treated with rituximab. Blood 2000;96:1184–1186.
25. Song KW, Mollee P, Patterson B, et al. Pure red cell aplasia due to parvovirus following treatment with CHOP and rituximab for B-cell lymphoma. Br J Haematol 2002;119:125–127.
26. Isobe Y, Sugimoto K, Shiraki Y, et al. Successful high-titer immunoglobulin therapy for persistent parvovirus B19 infection in a lymphoma patient treated with rituximab-combined chemotherapy. Am J Hematol 2004;77:370–373.
27. Huang C, Slater B, Rudd R, et al. First isolation of West Nile virus from a patient with encephalitis in the United States. Emerg Infect Dis 2002;8:1367–1371.
28. Mawhorter SD, Sierk A, Staugaitis SM, et al. Fatal West Nile Virus infection after rituximab/fludarabine–induced remission for non-Hodgkin's lymphoma. Clin Lymphoma Myeloma 2005;6:248–250.
29. Morris EC, Rebello P, Thomson KJ, et al. Pharmacokinetics of alemtuzumab used for in vivo and in vitro T-cell depletion in allogeneic transplantations: relevance for early adoptive immunotherapy and infectious complications. Blood 2003;102:404–406.
30. Rai KR, Freter CE, Mercier RJ, et al. Alemtuzumab in previously treated chronic lymphocytic leukemia patients who also had received fludarabine. J Clin Oncol 2002;20:3891–3897.
31. Osterborg A, Dyer MJ, Bunjes D, et al. Phase II multicenter study of human CD52 antibody in previously treated chronic lymphocytic leukemia. European Study Group of CAMPATH-1H Treatment in Chronic Lymphocytic Leukemia. J Clin Oncol 1997;15:1567–1574.
32. Keating MJ, Flinn I, Jain V, et al. Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: results of a large international study. Blood 2002;99:3554–3561.
33. Ferrajoli A, O'Brien SM, Cortes JE, et al. Phase II study of alemtuzumab in chronic lymphoproliferative disorders. Cancer 2003;98:773–778.
34. O'Brien SM, Kantarjian HM, Thomas DA, et al. Alemtuzumab as treatment for residual disease after chemotherapy in patients with chronic lymphocytic leukemia. Cancer 2003;98:2657–2663.
35. Martin SI, Marty FM, Fiumara K, et al. Infectious complications associated with alemtuzumab use for lymphoproliferative disorders. Clin Infect Dis 2006;43:16–24.
36. Nguyen DD, Cao TM, Dugan K, et al. Cytomegalovirus viremia during Campath-1H therapy for relapsed and refractory chronic lymphocytic leukemia and prolymphocytic leukemia. Clin Lymphoma 2002;3:105–110.
37. Laurenti L, Piccioni P, Cattani P, et al. Cytomegalovirus reactivation during alemtuzumab therapy for chronic lymphocytic leukemia: incidence and treatment with oral ganciclovir. Haematologica 2004;89:1248–1252.
38. Wendtner CM, Ritgen M, Schweighofer CD, et al. Consolidation with alemtuzumab in patients with chronic lymphocytic leukemia (CLL) in first remission–experience on safety and efficacy within a randomized multicenter phase III trial of the German CLL Study Group (GCLLSG). Leukemia 2004;18:1093–1101.
39. Faderl S, Thomas DA, O'Brien S, et al. Experience with alemtuzumab plus rituximab in patients with relapsed and refractory lymphoid malignancies. Blood 2003;101:3413–3415.
40. Kennedy B, Rawstron A, Carter C, et al. Campath-1H and fludarabine in combination are highly active in refractory chronic lymphocytic leukemia. Blood 2002;99:2245–2247.
41. Osterborg A, Fassas AS, Anagnostopoulos A, et al. Humanized CD52 monoclonal antibody Campath-1H as first-line treatment in chronic lymphocytic leukaemia. Br J Haematol 1996;93:151–153.
42. Lundin J, Kimby E, Bjorkholm M, et al. Phase II trial of subcutaneous anti-CD52 monoclonal antibody alemtuzumab (Campath-1H) as first-line treatment for patients with B-cell chronic lymphocytic leukemia (B-CLL). Blood 2002;100:768–773.
43. Dearden CE, Matutes E, Cazin B, et al. High remission rate in T-cell prolymphocytic leukemia with CAMPATH-1H. Blood 2001;98:1721–1726.
44. Keating MJ, Cazin B, Coutre S, et al. Campath-1H treatment of T-cell prolymphocytic leukemia in patients for whom at least one prior chemotherapy regimen has failed. J Clin Oncol 2002;20:205–213.
45. Uppenkamp M, Engert A, Diehl V, et al. Monoclonal antibody therapy with CAMPATH-1H in patients with relapsed high- and low-grade non-Hodgkin's lymphomas: a multicenter phase I/II study. Ann Hematol 2002;81:26–32.
46. Lundin J, Osterborg A, Brittinger G, et al. CAMPATH-1H monoclonal antibody in therapy for previously treated low-grade non-Hodgkin's lymphomas: a phase II multicenter study. European Study Group of CAMPATH-1H Treatment in Low-Grade Non-Hodgkin's Lymphoma. J Clin Oncol 1998;16:3257–3263.
47. Enblad G, Hagberg H, Erlanson M, et al. A pilot study of alemtuzumab (anti-CD52 monoclonal antibody) therapy for patients with relapsed or chemotherapy-refractory peripheral T-cell lymphomas. Blood 2004;103:2920–2924.

48. Lundin J, Hagberg H, Repp R, et al. Phase 2 study of alemtuzumab (anti-CD52 monoclonal antibody) in patients with advanced mycosis fungoides/Sezary syndrome. Blood 2003;101:4267–4272.
49. Gallamini A, Zaja F, Patti C, et al. Alemtuzumab (Campath-1H) and CHOP chemotherapy as first-line treatment of peripheral T-cell lymphoma: results of a GITIL (Gruppo Italiano Terapie Innovative nei Linfomi) prospective multicenter trial. Blood 2007;110:2316–2323.
50. Perez-Simon JA, Kottaridis PD, Martino R, et al. Nonmyeloablative transplantation with or without alemtuzumab: comparison between 2 prospective studies in patients with lymphoproliferative disorders. Blood 2002;100:3121–3127.
51. Ho AY, Pagliuca A, Kenyon M, et al. Reduced-intensity allogeneic hematopoietic stem cell transplantation for myelodysplastic syndrome and acute myeloid leukemia with multilineage dysplasia using fludarabine, busulphan, and alemtuzumab (FBC) conditioning. Blood 2004;104:1616–1623.
52. van Besien K, Artz A, Smith S, et al. Fludarabine, melphalan, and alemtuzumab conditioning in adults with standard-risk advanced acute myeloid leukemia and myelodysplastic syndrome. J Clin Oncol 2005;23:5728–5738.
53. Chakrabarti S, Mackinnon S, Chopra R, et al. High incidence of cytomegalovirus infection after nonmyeloablative stem cell transplantation: potential role of Campath-1H in delaying immune reconstitution. Blood 2002;99:4357–4363.
54. Lamba R, Carrum G, Myers GD, et al. Cytomegalovirus (CMV) infections and CMV-specific cellular immune reconstitution following reduced intensity conditioning allogeneic stem cell transplantation with alemtuzumab. Bone Marrow Transplant 2005;36:797–802.
55. Chakrabarti S, Mautner V, Osman H, et al. Adenovirus infections following allogeneic stem cell transplantation: incidence and outcome in relation to graft manipulation, immunosuppression, and immune recovery. Blood 2002;100:1619–1627.
56. Avivi I, Chakrabarti S, Milligan DW, et al. Incidence and outcome of adenovirus disease in transplant recipients after reduced-intensity conditioning with alemtuzumab. Biol Blood Marrow Transplant 2004;10:186–194.
57. Chakrabarti S, Avivi I, Mackinnon S, et al. Respiratory virus infections in transplant recipients after reduced-intensity conditioning with Campath-1H: high incidence but low mortality. Br J Haematol 2002;119:1125–1132.
58. Vu T, Carrum G, Hutton G, et al. Human herpesvirus-6 encephalitis following allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 2007;39:705–709.
59. Chakrabarti S, Osman H, Collingham K, et al. Polyoma viruria following T-cell-depleted allogeneic transplants using Campath-1H: incidence and outcome in relation to graft manipulation, donor type and conditioning. Bone Marrow Transplant 2003;31:379–386.
60. Heider U, Fleissner C, Zavrski I, et al. Treatment of refractory chronic lymphocytic leukemia with Campath-1H in combination with lamivudine in chronic hepatitis B infection. Eur J Haematol 2004;72:64–66.
61. Herbert KE, Prince HM, Westerman DA. Pure red-cell aplasia due to parvovirus B19 infection in a patient treated with alemtuzumab. Blood 2003;101:1654.
62. Crowley B, Woodcock B. Red cell aplasia due to parvovirus b19 in a patient treated with alemtuzumab. Br J Haematol 2002;119:279–280.
63. Sievers EL, Larson RA, Stadtmauer EA, et al. Efficacy and safety of gemtuzumab ozogamicin in patients with CD33-positive acute myeloid leukemia in first relapse. J Clin Oncol 2001;19:3244–3254.
64. Larson RA, Sievers EL, Stadtmauer EA, et al. Final report of the efficacy and safety of gemtuzumab ozogamicin (Mylotarg) in patients with CD33-positive acute myeloid leukemia in first recurrence. Cancer 2005;104:1442–1452.
65. Scott DL, Kingsley GH. Tumor necrosis factor inhibitors for rheumatoid arthritis. N Engl J Med 2006;355:704–712.
66. Bongartz T, Sutton AJ, Sweeting MJ, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA 2006;295:2275–2285.
67. Wallis RS, Broder M, Wong J, et al. Reactivation of latent granulomatous infections by infliximab. Clin Infect Dis 2005;41(Suppl 3):S194–198.
68. Jacobsohn DA, Hallick J, Anders V, et al. Infliximab for steroid-refractory acute GVHD: a case series. Am J Hematol 2003;74:119–124.
69. Marty FM, Lee SJ, Fahey MM, et al. Infliximab use in patients with severe graft-versus-host disease and other emerging risk factors of non-Candida invasive fungal infections in allogeneic hematopoietic stem cell transplant recipients: a cohort study. Blood 2003;102:2768–2776.
70. Couriel D, Saliba R, Hicks K, et al. Tumor necrosis factor-alpha blockade for the treatment of acute GVHD. Blood 2004;104:649–654.
71. Busca A, Locatelli F, Marmont F, et al. Recombinant human soluble tumor necrosis factor receptor fusion protein as treatment for steroid refractory graft-versus-host disease following allogeneic hematopoietic stem cell transplantation. Am J Hematol 2007;82:45–52.
72. Wolff D, Roessler V, Steiner B, et al. Treatment of steroid-resistant acute graft-versus-host disease with daclizumab and etanercept. Bone Marrow Transplant 2005;35:1003–1010.
73. Przepiorka D, Kernan NA, Ippoliti C, et al. Daclizumab, a humanized anti-interleukin-2 receptor alpha chain antibody, for treatment of acute graft-versus-host disease. Blood 2000;95:83–89.
74. Willenbacher W, Basara N, Blau IW, et al. Treatment of steroid refractory acute and chronic graft-versus-host disease with daclizumab. Br J Haematol 2001;112:820–823.
75. Srinivasan R, Chakrabarti S, Walsh T, et al. Improved survival in steroid-refractory acute graft versus host disease after non-myeloablative allogeneic transplantation using a daclizumab-based strategy with comprehensive infection prophylaxis. Br J Haematol 2004;124:777–786.
76. Perales MA, Ishill N, Lomazow WA, et al. Long-term follow-up of patients treated with daclizumab for steroid-refractory acute graft-vs-host disease. Bone Marrow Transplant 2007;40:481–486.
77. Funke VA, de Medeiros CR, Setubal DC, et al. Therapy for severe refractory acute graft-versus-host disease with basiliximab, a selective interleukin-2 receptor antagonist. Bone Marrow Transplant 2006;37:961–965.
78. Schmidt-Hieber M, Fietz T, Knauf W, et al. Efficacy of the interleukin-2 receptor antagonist basiliximab in steroid-refractory acute graft-versus-host disease. Br J Haematol 2005;130:568–574.

Immunomodulating Monoclonal Antibodies and Hematologic Malignancies

To obtain credit, you should first read the journal article. After reading the article, you should be able to answer the following, related, multiple-choice questions. To complete the questions and earn continuing medical education (CME) credit, please go to **http://www.medscape.com/cme/jnccn**.

Credit cannot be obtained for tests completed on paper, although you may use the worksheet below to keep a record of your answers. You must be a registered user on Medscape.com. If you are not registered on Medscape.com, please click on the New Users: Free Registration link on the left hand side of the website to register.

Only one answer is correct for each question. Once you successfully answer all post-test questions you will be able to view and/or print your certificate. For questions regarding the content of this activity, contact the accredited provider, CME@medscape.net. For technical assistance, contact CME@webmd.net.

American Medical Association's Physician's Recognition Award (AMA PRA) credits are accepted in the US as evidence of participation in CME activities. For further information on this award, please refer to http://www.ama-assn.org/ama/pub/category/2922.html. The AMA has determined that physicians not licensed in the US who participate in this CME activity are eligible for *AMA PRA Category 1 Credits™*. Through agreements that the AMA has made with agencies in some countries, AMA PRA credit is acceptable as evidence of participation in CME activities. If you are not licensed in the U.S. and want to obtain an AMA PRA CME credit, please complete the questions online, print the certificate and present it to your national medicalassociation.

1. Which one of the following is the *most likely* action of rituximab when used for hematologic malignancies?
   A. Depletion of T cells
   B. Depletion of peripheral blood B lymphocytes
   C. Reduction in circulating immunoglobulin levels
   D. Impairment of cell-mediated immunity

2. Which one of the following is *most likely* to be the US Food and Drug Administration (FDA)-approved indication for use of alemtuzumab for hematologic malignancies?
   A. B-cell chronic lymphocytic lymphoma (CLL)
   B. Non-Hodgkin's lymphoma
   C. Hodgkin's lymphoma
   D. Cryoglobulinemia

3. The prevalence of opportunistic infections associated with alemtuzumab is best described by which one of the following?
   A. 10%
   B. 20%
   C. 30%
   D. 40%

4. Which one of the following is the *most likely* major toxicity reported for gemtuzumab?
   A. Bleeding tendency
   B. Aspergillosis
   C. Prolonged myelosuppression
   D. Candidiasis

5. Which one of the following *best describes* the incidence of serious infections in patients receiving infliximab on the basis of national registry data from the United Kingdom and Germany?
   A. 1.0-2.0 per 100 patient-years
   B. 2.1-3.1 per 100 patient-years
   C. 5.2-6.2 per 100 patient-years
   D. 10.0-12.0 per 100 patient-years

Activity Evaluation

1. The activity supported the learning objectives.
   Strongly Disagree 1 2 3 4 5 Strongly Agree
2. The material was organized clearly for learning to occur.
   Strongly Disagree 1 2 3 4 5 Strongly Agree
3. The content learned from this activity will impact my practice.
   Strongly Disagree 1 2 3 4 5 Strongly Agree
4. The activity was presented objectively and free of commercial bias.
   Strongly Disagree 1 2 3 4 5 Strongly Agree

To obtain credit go to Medscape online at: http://www.medscape.com/CME/JNCCN