Immunosuppression Associated With Novel Chemotherapy Agents and Monoclonal Antibodies

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The introduction of novel agents to the therapeutic armamentarium for oncologic, rheumatologic, and neurologic disorders has resulted in major clinical advances. These agents impact immune function, resulting in a discrete spectrum of infectious complications. Purine analogues and alemtuzumab alter cell-mediated immunity, resulting in opportunistic viral/fungal infections. Herpes zoster incidence increases with bortezomib. Hepatitis B reactivation may occur with rituximab. Cases of progressive multifocal leukoencephalopathy have occurred following monoclonal antibody therapy. Tumor necrosis factor-α inhibitor therapy is complicated by tuberculosis reactivation and fungal infections. We summarize the impact of these therapies on pathogenesis and spectrum of infection complicating their usage.

**Keywords.** fludarabine; alemtuzumab; bortezomib; hepatitis B; tumor necrosis factor-α inhibitors.

Novel therapeutic agents developed for hematologic, rheumatologic, and neurologic disorders have significant impact on disease course but also on immune function resulting in unique infectious complications (Table 1). We will review the pathogenesis, spectrum, and therapy of infection with purine analogues, alemtuzumab, bortezomib; monoclonal antibodies for neurologic disorders; tumor necrosis factor α (TNF-α) inhibitors; and hepatitis B virus reactivation.

**PURINE ANALOGUES**

Common bacterial and opportunistic infections occur in lymphoproliferative disorder patients receiving purine analogues (fludarabine, cladribine, pentostatin). Pathogenesis is related to T-cell defects, occurring early in therapy and persisting 1–2 years after discontinuation. Risk factors for infection in fludarabine-treated chronic lymphocytic leukemia (CLL) patients include advanced disease stage, prior therapy, therapeutic response, elevated creatinine, hemoglobin <12 g/dL, and low immunoglobulin G (IgG) levels [1, 2]. More infections occurred with fludarabine compared to alkylator therapy in CLL patients, especially herpesvirus infections (herpes simplex [HSV], herpes zoster [HZ]) [3]. *Aspergillus, Candida*, mycobacterial, and *Pneumocystis* infections were uncommon. Adding cyclophosphamide to fludarabine (FC), compared to fludarabine, resulted in comparable rates of severe and opportunistic infections in treatment-naive patients [4]. In previously treated CLL patients receiving FC, 57% had infections or fever of unknown origin, including 26% herpesvirus and 7% fungal infections; 74% of infections occurred in the first 3 months of therapy [5]. A 20% grade 3/4 infection rate, including localized herpesvirus and 2 *Pneumocystis* cases, occurred with initial rituximab plus fludarabine (FR) CLL therapy [6]. Fludarabine, cyclophosphamide, rituximab (FCR) CLL therapy resulted in major (pneumonia, septicemia, etc) and herpesvirus infection rates of 2.6% and 1%, respectively, in treatment-naive, and 16% and 5%, respectively, in previously treated patients [7, 8]. Similar infection trends occur with cladribine- or pentostatin-based regimens [9, 10].
A M L T U Z U M A B

The anti-CD52 antibody alemtuzumab causes cell-mediated immune defects that develop early in treatment and persist >9 months after discontinuation, having no correlation with cumulative dose or administration route. In an alemtuzumab trial for previously treated CLL patients, 27% had grade 3/4 infections (Candida, Aspergillus, Zygomycetes, Cryptococcus, Pneumocystis, Listeria, cytomegalovirus [CMV] reactivation) [11]. In 410 alemtuzumab-treated lymphoproliferative disorder patients, 95/262 (36%) infections were bacterial, and 167 (64%) opportunistic, with HSV and CMV reactivation most common (32% and 31%, respectively) [12].

Alemtuzumab consolidation therapy has been studied in CLL trials. In one with initial fludarabine or FC therapy, followed 2 months later by alemtuzumab consolidation, 7/11 patients developed grade 3/4 infections (4 CMV reactivation, aspergillosis, tuberculosis, HZ), resulting in study termination [13]. In another with alemtuzumab consolidation 5 months after induction therapy response, 9/41 (22%) patients had CMV reactivation [14]. Alemtuzumab consolidation was used in 2 oncology cooperative group trials [15–17]. Fludarabine induction was followed 2 months later by alemtuzumab in 1, with 8/57 enrollees developing CMV reactivation, 1 fatal, resulting in weekly CMV polymerase chain reaction (PCR) implementation [15, 16]. In the other, induction FR was followed by alemtuzumab consolidation 3 months later, with 7 infectious deaths in induction responders (EBV viremia/hepatitis, transfusion-associated graft-vs-host disease, Listeria meningitis, Legionella pneumonia, Pneumocystis pneumonia, sepsis, viral meningitis) [17]. These patients had normal neutrophil counts but median lymphocyte counts <1.0 × 10⁹/L following induction FR and preceding alemtuzumab. Comparing fludarabine or FR induction, or fludarabine induction with alemtuzumab consolidation (FA), infections, especially CMV and Pneumocystis, were more common with FA than fludarabine or FR [16].

Antimicrobial prophylaxis recommendations have been developed [18, 19]. With fludarabine or FR, antiviral (HSV, HZ) prophylaxis is considered for the elderly or those with low CD4 counts. Antiviral and Pneumocystis prophylaxis should be used with FC or FCR. The major infectious complication with alemtuzumab is CMV reactivation, occurring in 4%–30% of patients, commonly early in therapy when patients are lymphopenic and neutropenic [18]. Thus, antiviral, antifungal, and Pneumocystis prophylaxis should be used, plus weekly/biweekly quantitative CMV PCR monitoring. CMV prophylaxis with ganciclovir may be considered [20]. Preemptive ganciclovir may be used with CMV viremia or increasing viral load, for 14–21 days until symptoms resolve and PCR tests are negative. CMV surveillance and preemptive therapy has reduced the incidence of symptomatic CMV reactivation from 30% to 9% [18].

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<th>Table 1. Novel Agents and Unique Toxicities</th>
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<td><strong>Agent</strong></td>
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<td>Purine analogues (Fludarabine, cladribine, pentostatin)</td>
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<td>Alemtuzumab</td>
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Abbreviations: CMV, cytomegalovirus; HSV, herpes simplex virus; HZ, herpes zoster virus; TNF, tumor necrosis factor.

BO RT E Z O M I B

Bortezomib impacts T-cell immunity via nuclear factor-κ-B inhibition and alterations in dendritic/T-cell subset numbers and function. An increased incidence of HZ, ranging from 13% to 22%, occurs in bortezomib-treated myeloma patients, most early in treatment [21]. Although there was no association between HZ occurrence and baseline hemoglobin, platelet count, absolute neutrophil count (ANC), or absolute lymphocyte count (ALC), prior therapies, or performance status, median ALC and ANC at HZ occurrence were lower in bortezomib-treated patients (P < .001). HZ incidence was 10.3%, with median time to occurrence of 39 days, in bortezomib-treated relapsed/refractory mantle cell lymphoma patients, with age ≥65 years the only baseline predictive factor [22].

HEPATITIS B VIRUS (HBV) REACTIVATION

HBV reactivation is considered with reappearance of active inflammatory disease in: HB surface antigen carriers (HBsAg+); HB core antibody+/-; HB surface antibody--; undetectable HBV DNA); occult HBV infection (−HBsAg; HB core antibody+; HB
surface antibody−); patients convalescing from prior infection (HBsAg−; HB core antibody+; HB surface antibody+). Reactivation elevation and appearance/increase in HBV DNA may also be examined. Reactivation following chemotherapy may occur anytime, with HBsAg+ patients at greatest risk. Loss of HB surface antibody is a risk factor for reactivation. Recommendations for specific screening tests vary, though all include HBsAg testing. Passive transfer of HB core antibody occurs with intravenous immunoglobulin (IVIG) usage.

Populations at risk for reactivation are broad [23, 24]. Although rituximab is the most recognized agent for HBV reactivation, it may occur with alemtuzumab, ibritumomab tiuxetan, bendamustine, chlorambucil, imatinib, corticosteroids, anthracyclines, cyclophosphamide, 5FU, docetaxel, and temozolomide. Risk factors for reactivation include male gender, younger age, lymphoma diagnosis, and HBeAg+ [25]. Lamivudine is used most for HBV reactivation, with adefovir, entecavir, telbivudine, and tenofovir as alternative agents. Development of resistance is an issue with single drug therapy. However, use of single agent vs combination therapy has not been prospectively examined. Although optimal therapy duration is unclear, antivirals may be initiated 1–2 weeks prior to therapy and continued for 6 months after treatment completion, with monitoring of HBV DNA and transaminases. The role of prophylaxis or preemptive therapy remains controversial.

**MONOClonAL ANTIBodies AND NEUROLOGIC DISORDERs**

Multiple sclerosis, optic neuritis, and demyelinating neuropathy have been reported with TNF-α inhibitors, with 30% increased risk [26]. Treatment includes corticosteroids, IVIG, plasmapheresis, and cessation of the biologic agent.

Most progressive multifocal leukoencephalopathy (PML) cases occur in patients who test positive for human immunodeficiency virus (HIV). In patients with rheumatologic/neurologic disorders, PML occurrence has mainly been associated with natalizumab (used for multiple sclerosis) and less with rituximab, alemtuzumab, or efalizumab, with prevalence of 0.02%–0.20% [27]. Efalizumab (for plaque psoriasis) was withdrawn from the market in 2009 for this reason.

**TUMOR NECROSIS FACTOR α INHIBITORS**

New biologic agents developed for autoimmune disorders include TNF-α inhibitors (etanercept, infliximab, adalimumab, golimumab, certolizumab), interleukin (IL)-1 antagonist anakinra, IL-6 antagonist tocilizumab, and abatacept (T-cell modulator). As TNF is crucial in intracellular pathogen defense, there is a greater risk for infection with *Mycobacteria, Listeria, Legionella, Salmonella, Nocardia*, endemic fungi, *Pneumocystis, Candida, Aspergillus, Zygomycetes*, hepatitis B/C, and herpesviruses [28]. In a large series of rheumatoid arthritis (RA) patients receiving TNF-α inhibitors, 1-year infection rate/100 person-years was 14.2 in those age ≥65 years and 4.8 in those age <65 [29]. Infection rates were highest with infliximab, compared to etanercept or adalimumab.

Reactivation of latent tuberculosis is a significant issue with TNF-α inhibitors [30]. Tuberculosis risk is 2- to 4-fold higher with RA and further increased 4- to 10-fold in patients receiving these agents. Disease pattern is similar to that in immunosuppressed patients (56%–62% extrapulmonary infections and 24%–28% disseminated infections, compared to 18% and <2%, respectively, in nonimmunosuppressed patients). Highest infection rates are with adalimumab and lowest with etanercept. As infection rates remain stable throughout etanercept therapy, it is thought that these infections represent newly acquired, vs reactivation, disease. With infliximab, infection rates are highest early in treatment, likely representing latent infections. Comparing infliximab and etanercept, median time to tuberculosis onset is 16 and 60 weeks and monthly reactivation rates are 20% and 2%, respectively. Pretherapy screening may be by interferon-based assays or tuberculin skin test (TST), with TST reaction ≥5 mm positive. Treatment recommendations for latent tuberculosis are 9 months of isoniazid for either positive TST, past history of untreated tuberculosis, or chest X-ray suggestive of past tuberculosis [31]. Alternative treatment regimens include: 6 months of isoniazid or 4 months of rifampicin; 6 months isoniazid with 2 months of rifampicin/pyrazinamide; weekly isoniazid-rifapentine for 12 weeks. Timing of treatment ranges from concurrent administration to waiting 1–2 months after completing antituberculous therapy. Paradoxical reactions, similar to immune reconstitution inflammatory syndrome, are uncommon and related to recovery of TNF-dependent inflammation.

Patients on TNF-α inhibitors are also at increased risk of fungal/viral infections [32–34]. Infliximab is associated with 2-fold increased risk of histoplasmosis, coccidiodomycosis, candidiasis, listeriosis, nocardiosis, and nontuberculous mycobacterial infections. Infection risk is 3-fold greater with infliximab than etanercept. Similar to mycobacterial infections, 72% occurred within 90 days of infliximab initiation, vs 28% for etanercept, with median time from treatment initiation to infection of 190 and 511 days, respectively. HZ infections are more common [34]. Patients should be screened for hepatitis B and C prior to treatment initiation.

TNF-α inhibitors have also been associated with increased risk of malignancy [35, 36]. The standardized incidence ratio (SIR) of cancer in RA patients, compared with the general population, was 1.26 [35]. An increased cancer risk was found in TNF-α inhibitor-treated patients compared with the general population, including lymphoproliferative disorders (SIR 2.06,
4.81 for non-Hodgkin lymphoma and Hodgkin lymphoma, respectively), nonmelanoma skin cancer (squamous/basal cell, SIR 1.84), and lung cancer (SIR 1.47), but not colon cancer (SIR 1.08). However, among TNF-α inhibitor-treated vs non-treated RA patients, an increased colon risk (hazard ratio 3.52) was found.

**SUMMARY**

The addition of a variety of novel agents to the therapeutic armamentarium for oncologic, rheumatologic, and neurologic disorders has lead to major clinical advances. However, many of these agents also impact immune function, resulting in a discrete spectrum of infectious complications, necessitating approaches for screening and/or prophylaxis to minimize these complications. In future development of such agents, although efficacy remains a primary endpoint, related issues as subsequent infections also need to be taken into consideration.

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**References**


