Infections are a primary cause of death in patients with chronic lymphocytic leukemia (CLL). Such individuals are particularly susceptible to infectious complications stemming from immune deficits associated with the primary disease process and with immunosuppression secondary to treatment. Although the recent availability of new treatment modalities and more aggressive therapies are improving outcomes for patients with CLL, standardized approaches are needed so that nurses can monitor for and manage infections. The aim is overall reduction in morbidity and mortality, as well as improvement in quality of life. The current pharmacologic therapies for CLL are alkylating agents, purine nucleoside analogs, monoclonal antibodies, and combinations of those therapies, which may present their own unique risks for and different spectra of infectious events. This article provides an overview of the known risks for developing infections in CLL, as well as nursing guidelines for monitoring and managing patients with CLL.

At a Glance

- Patients with chronic lymphocytic leukemia (CLL) are susceptible to infectious complications caused by immune deficits associated with the primary disease process and immunosuppression secondary to treatment.
- Infectious complications remain a primary cause of morbidity and mortality in patients with CLL; nursing assessments and real-time patient management are essential to decreasing infection-related morbidity and mortality.
- Nurses play a key role in providing patient and caregiver education and in facilitating patient adherence to anti-infective treatments to minimize infectious complications.

In 2007, an estimated 15,340 individuals in the United States will be diagnosed with chronic lymphocytic leukemia (CLL) and 4,500 patients will die as a result of the disease (Jemal et al., 2007). CLL is the second most commonly diagnosed leukemia in Western countries, occurring primarily in middle-aged and older adults, with increasing frequency in successive decades of life.

The most common presenting symptom in CLL is lymphadenopathy, although some patients report fever, weight loss, or night sweats (Rai et al., 1975). About 70%–80% of patients are asymptomatic and are diagnosed after a routine blood count shows lymphocytosis (Abbott, 2006; Oscier et al., 2004). A definitive diagnosis of CLL is based on the combination of lymphocytosis and characteristic lymphocyte morphology and immunophenotype (Oscier et al.). Bone marrow examination may be used to aid in the diagnosis of CLL and can be particularly helpful in determining the cause of cytopenias, as well as providing prognostic information and serial assessment of response to therapy.

Stage of CLL is determined based on the Rai and Binet clinical staging systems in the United States and Europe, respectively (Binet et al., 1981; Rai et al., 1975) (see Figure 1). The staging systems are used to categorize the extent of lymphocytosis, presence of cytopenias, and organ involvement; they have been used to predict the natural course of disease and the need for therapy. An understanding of the disease processes in CLL, including the development of cytopenias delineated in the staging criteria, allows for more effective nursing care. Patient survival varies based on stage of disease and ranges from less...
Infections in Patients With Chronic Lymphocytic Leukemia

Two monoclonal antibodies, rituximab and alemtuzumab, are emerging as effective therapies for CLL. They act on specific cell surface antigens CD20 and CD52, respectively (Cartron, Watier, Golay, & Solal-Celigny, 2004; Waldmann & Hale, 2005). Rituximab may potentiate the activity of chemotherapy when used in combination with or as a maintenance agent after fludarabine (Byrd et al., 2003). Alemtuzumab is approved by the U.S. Food and Drug Administration for treatment of previously untreated and relapsed or refractory CLL (Bayer HealthCare Pharmaceuticals Inc., 2007; National Comprehensive Cancer Network [NCCN], 2006). The pivotal alemtuzumab study in 93 heavily pretreated patients with fludarabine-refractory CLL reported an overall response of 33%, with median overall survival of 16 months among all patients and 32 months among responders (Keating et al., 2002).

Overall, the main therapies for CLL include chemotherapy (alkylating agents and purine nucleoside analogs), monoclonal antibodies, and combinations of those agents. Although the mechanisms of action for the regimens are distinctly different, they all have the potential to increase vulnerability to infections.

Factors Contributing to the Risk of Infection

As many as 50% of patients with CLL have recurrent infection at some point during the course of their disease, resulting in death for more than 50% of those patients (Molina, 1994). An abundance of literature addresses the potential risks of developing infections with respect to patient status, stage of disease, and treatment (see Figure 2). Nurses should be aware of the risk factors prior to and while administering treatment.

Age is a major factor to be considered in a patient’s ability to tolerate treatment without undue toxicity. Patients 70 years of age or older are reported to have a higher incidence and greater severity of toxicities than younger patients. Moreover, older adults with CLL, compared with younger patients, may have an inherent susceptibility to infections that is exacerbated by the disease process (Ravandi & O’Brien, 2006).

Hypogammaglobulinemia, defined as depressed immunoglobulin levels, has been considered the primary risk factor for severe infections in patients with CLL, although retrospective analysis showed that the number of prior chemotherapy regimens, rather than hypogammaglobulinemia, had the strongest impact on the risk of bacterial and certain viral infections (Hensel, Kornacker, Yammenni, Egerer, & Ho, 2003; Molica, 1994; Morra, Nosari, & Montillo, 1999). Humoral immunodeficiency long has been recognized as the key defect that predisposes patients with CLL to infection. Recent observations have shown that defects in T cells and natural killer cells, neutrophil dysfunction, and defects in the complement system also contribute to immunodeficiency during CLL (Hensel et al.; Molica; Morra et al.; Ravandi & O’Brien, 2006; Wadhwa & Morrison, 2006). The complement system is critical in protecting the body against infection with encapsulated organisms (e.g., Haemophilus influenzae) through opsonization and neutrophil activation. Defects in the system place patients at risk for infection by the more virulent encapsulated strains of pneumococci and H. influenzae.

Aside from inherent risks, comorbid conditions and immunosuppression secondary to cytotoxic therapy or corticosteroids...
are factors that contribute to infection during CLL (Morra et al., 1999; Morris et al., 2003). Comorbidities are more likely to be present in older individuals and may affect patients’ ability to tolerate treatment (Wierda & O’Brien, 2006).

As the treatment paradigm has changed following the introduction of novel agents, including purine analogs and monoclonal antibodies, a unique spectrum of organisms is now part of the growing list of opportunistic infections affecting patients with CLL treated with the newer agents. *Pneumocystis jiroveci* (formerly known as *P. carinii*), *Aspergillus*, *Candida albicans*, varicella zoster virus (VZV), and herpes simplex virus (HSV) are among them (Morris et al., 2001). Although highly active against leukemia, newer therapeutic agents may increase the risk of infection over earlier therapies because of increased incidence and severity of myelosuppression, which may linger for months following cessation of treatment. For example, cell-mediated immune dysfunction from fludarabine is thought to be responsible for a high incidence of infectious events (Sandherr et al., 2006; Sudhoff, Arning, & Schneider, 1997). Cellular immunodeficiency after therapy with purine analogs may outlast exposure by months, increasing the risk of viral infections.

**Monitoring and Managing Infections**

**Baseline Evaluation and Monitoring Techniques**

All patients being treated or observed for CLL should be evaluated for baseline health status and risk of infection before initiation of treatment. Evaluation should include a review of medical records for health and social history, history of the disease, comorbidities, concomitant medications, and history of previous infectious episodes. Patients also may be screened for bacterial, fungal, and viral infections prior to initiation of therapy (see Table 1). Bacterial and fungal infections may be examined through colonization techniques, whereas serology screens may be performed to assess viral titer levels. During treatment, nurses should evaluate patients’ status at each visit. Complete vital signs, including temperature, must be assessed, and nurses should interview patients for any signs or symptoms of infection during the interval since the previous treatment. Nurses play an integral role in patient education. Thus, at each visit, nurses should reinforce the importance of communication between patients and caregivers concerning the development of neutropenia, potential risks for infections, and signs and symptoms to be reported to the clinical team (Breed, 2003; Nirenberg et al., 2006).

Most patients with CLL eventually experience neutropenia because of progressive marrow involvement or as a result of myelosuppressive therapies (Wadhwa & Morrison, 2006). The neutropenic nadir, or the period during which the neutrophil count is at its lowest level, is associated with increased susceptibility to bloodborne infections (e.g., bacteremia, septicemia) (Wadhwa & Morrison). The neutropenic nadir can be anticipated, and nurses should advise patients of the time period during which the nadir will occur so that they can adapt social and work activities and take appropriate action to avoid infection (Shelton, 2003). Healthcare professionals should consider administering support therapy with growth factors, such as granulocyte–colony-stimulating factor (G-CSF) or granulocyte macrophage-colony-stimulating factor (GM-CSF), during the anticipated neutropenic periods in patients who are at high risk for developing infections (Nirenberg et al., 2006).

Although some treatment modalities (e.g., monoclonal antibodies) may cause fever during or immediately after infusion, febrile patients with CLL should be considered to have an infection until proven otherwise. The disease itself usually is not associated with prolonged fever, absent progressive disease or infection. Fever and chills or rigors are common infusion-related reactions associated with agents such as rituximab and alemtuzumab, especially during the first several infusions.

In patients presenting with a fever of unknown origin while receiving alemtuzumab-based therapy, the possibility of cytomegalovirus (CMV) reactivation should be considered (see later section on monoclonal antibodies). When a fever is observed outside the context of infusion-related toxicities, careful physical examination of the patient and systems, as well as appropriate diagnostic testing and cultures, must be completed to determine the cause of the fever. Diagnostic evaluations should include complete blood count (CBC) with differentials, blood chemistry and/or cultures for bacterial or fungal infections, and a chest radiograph in patients presenting with respiratory signs or symptoms (NCCN, 2005). Urinalysis and culture should be performed when symptoms of urinary tract infection are present. If respiratory viral infections are suspected, viral cultures and viral antigen assays of the nasopharyngeal secretions may be required, particularly during the influenza season or during local outbreaks (NCCN, 2005).

For patients with fever and neutropenia, nurses should be prepared to start antibiotics immediately while diagnostic test results are pending. Providing patients with a prescription for an oral broad-spectrum antibiotic to keep at home and take on instruction from a physician or nurse may help facilitate prompt initiation of antibiotic therapy. However, nurses should emphasize to patients the need to withhold antibiotic therapy until notification from or prior discussion with the clinical team. In treatment centers where oral antibiotics are not sent home with patients routinely, nurses should advise patients and caregivers to promptly contact the clinical team at the first sign of a fever;
nurses then can instruct patients to return to the hospital to receive antibiotic treatment, as needed.

**Anti-Infective Treatments and Prophylaxis**

The spectrum of infections associated with specific CLL therapies consists of bacterial, viral, and opportunistic infections, including reactivation of latent viruses such as herpes and hepatitis B. NCCN (2005) offers guidelines for site-specific infection evaluation and treatment recommendations in patients with cancer in the United States. Similar directives are available in the United Kingdom, although each institution has its own set of guidelines and policies. Table 2 lists the anti-infective agents commonly used in the treatment and prophylaxis of infectious events that may be observed in patients with CLL. Regardless of the disease status or therapeutic regimen administered, antiviral prophylaxis may benefit patients who present with low baseline CD4 levels (< 50/mcl) (Wadhwa & Morrison, 2006). In patients with early-stage CLL and in those receiving first-line therapies, antimicrobial prophylaxis may not be necessary or cost effective if they have normal or only minimally decreased immunoglobulin levels. Prior to initiating anti-infective therapy, nurses should check patients’ medical records and verify verbally with patients any history of medication allergies, particularly to antibiotics.

Nurses must provide counseling to patients who are taking antibiotics or antiviral medications with regard to potential side effects, to whom side effects should be reported, and how adverse effects of medications should be managed. Nurses should ensure that patients and caregivers understand that some side effects of antibiotics and antiviral therapies may be similar to the side effects from CLL therapy. Contacting a nurse when side effects occur will help patients manage them more effectively without interrupting antineoplastic or anti-infective therapy.

The most common side effects of antibiotics are gastrointestinal (e.g., nausea, vomiting, diarrhea). If diarrhea is watery or persistent, it may be of an infectious nature and a stool culture should be obtained for *Clostridium difficile* or other enteric pathogens (NCCN, 2005). Some antibiotics, including metronidazole and clarithromycin, also may cause taste changes and subsequent anorexia. Women on antibiotic therapy may develop vaginal yeast infections, usually of the *C. albicans* strain; both men and women can develop oral candidiasis (thrush). Sulfonamides can cause leukopenia (Beers, Berkow, & Jones, 2006). Antibiotics are not effective against viral infections, but when patients have a bacterial infection in addition to a viral infection, concomitant antibiotics may be necessary. Antiviral medications generally do not cause diarrhea but can cause nausea, vomiting, and anorexia. Ganciclovir and valganciclovir can cause leukopenia (Beers et al.). Nursing assessments for patient tolerance and adherence are key components in determining the effectiveness of anti-infective treatment. Nurses should consider administering antiemetic treatment to facilitate patient tolerance and adherence, as well as assess the timing of administration of anti-infective treatments (e.g., at mealtime), which may improve patient adherence (Blash, 2002).

Several classes of antifungal agents are available, but the structure and chemical makeup of fungi, in addition to their ability to develop drug resistance, make fungal infections difficult to manage. Antifungal drugs may be applied directly to fungal infections of the skin or other surfaces, such as the vagina and oral mucosa. Antifungal drugs also may be taken by mouth or injected when needed to treat more serious infections. Susceptibility testing forazole resistance is used increasingly to guide the management of candidiasis, especially in situations when patients fail to respond to initial empirical therapy. Most *Candida* isolates appear to remain susceptible to amphotericin

---

**Table 1. Monitoring Strategies for Nurses**

<table>
<thead>
<tr>
<th>TYPE OF INFECTION</th>
<th>MONITORING STRATEGIES FOR NURSES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial</strong></td>
<td></td>
</tr>
<tr>
<td>Latent tuberculosis</td>
<td>• Baseline tuberculosis skin test in endemic areas</td>
</tr>
<tr>
<td></td>
<td>• Treatment if tuberculosis test (+) and exclude active tuberculosis</td>
</tr>
<tr>
<td><strong>Fungal</strong></td>
<td></td>
</tr>
<tr>
<td>General fungal infections</td>
<td>• Screen for colonization prior to therapy by sputum culture and/or nasal swab</td>
</tr>
<tr>
<td></td>
<td>• Computed tomography of chest or sinuses if past history of invasive fungal infection or colonization</td>
</tr>
<tr>
<td><em>Pneumocystis jiroveci</em> (formerly <em>P. carinii</em>)</td>
<td>• CD4 count at baseline and during treatment</td>
</tr>
<tr>
<td><strong>Viral</strong></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>• Screen for hepatitis B surface antigen and core antibody prior to treatment.</td>
</tr>
<tr>
<td>Herpes viruses (varicella zoster virus, herpes simplex virus)</td>
<td>• Little value to varicella zoster virus or herpes simplex virus titers</td>
</tr>
<tr>
<td></td>
<td>• Monitor for appearance of varicella zoster virus or herpes simplex virus lesions.</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>• Baseline cytomegalovirus reactivation status prior to therapy</td>
</tr>
<tr>
<td></td>
<td>• Weekly quantitative CMV tests during therapy</td>
</tr>
</tbody>
</table>

### Table 2. Nursing Management of Infections and Nursing Guidelines for Prophylaxis and Anti-Infective Medication

<table>
<thead>
<tr>
<th>INFECTIOUS ORGANISM</th>
<th>TREATMENTS</th>
<th>PROPHYLAXIS</th>
<th>TREATMENT</th>
<th>DURATION</th>
<th>POTENTIAL SIDE EFFECTS</th>
<th>NURSING INTERVENTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial, gram positive</strong></td>
<td>Alkylation agents</td>
<td>Amoxicillin + clavulanic acid (500 mg TID or 875 mg BID) or TMP/SMX, DS, TMW</td>
<td>IV broad-spectrum antibiotics (cephalosporin + aminoglycoside)</td>
<td>Prophylaxis usually is not needed in early-stage CLL during alkylation therapy in absence of other infection risks; begin at onset of signs or symptoms of infection (fever, chills). During periods of neutropenia in pretreated patients.</td>
<td>Nausea, vomiting, diarrhea; allergy with potential for anaphylaxis</td>
<td>• If oral dosing, instruct patient to take entire course. • Report signs and symptoms of diarrhea or superinfections. • Antiemetic therapy (with or without food) • May use analgesics with caution</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Fludarabine, Cladribine, Pentostatin</td>
<td>Consider G-CSF or GM-CSF in patients at high risk for infection.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Alemtuzumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Bacterial, gram negative** | | | | | | |
| **Escherichia coli** | | | Ciprofloxacin (500 mg BID) | | Nausea, nervousness, tremors, seizures | • May take ciprofloxacin with food to decrease nausea |
| **Klebsiella species** | | | | | | |
| **Enterobacter species** | | | | | | |
| **Haemophilus influenzae** | | | | | | |

**Bacterial, latent tuberculosis** | | | Isoniazid (300 mg per day) | 12 months | Peripheral neuropathy | • Report signs and symptoms of hepatitis. • Avoid alcohol consumption. |

**Viral, cytomegalovirus (CMV)** | Alemtuzumab | Valganciclovir (450 mg BID) | IV ganciclovir (5 mg/kg BID for 14 days) If no response, foscarnet (60 mg/kg TID or 90 mg/kg BID) | Initiate treatment after single positive quantitative CMV DNA result. Treat for at least one week or until quantitative CMV polymerase chain reaction assay is negative and patient is asymptomatic. | Leukopenia, decreased renal function, seizures, electrolyte wasting | • Report signs and symptoms of superinfection or bleeding. • Evaluate BUN, creatinine, and electrolytes every two weeks. |

**Viral, herpes viruses** | Fludarabine, Cladribine, Pentostatin | Famciclovir (500 mg BID), Valacyclovir (500 mg QD), or Acyclovir (400 mg BID) | Famciclovir (500 mg BID), Valacyclovir (1–3 g TID), or Acyclovir (400 mg BID) | Up to six months after therapy Consider prophylaxis for any patient with initial CD4 count < 50/ml. | Nausea, vomiting, diarrhea, headaches | • Monitor lesions for progression or resolution. • Monitor BUN and creatinine. • May take with food or on an empty stomach • If genital herpes are present, avoid sexual contact and use condoms even without active sores. |

| BID—two times per day; BUN—blood urea nitrogen; CLL—chronic lymphocytic leukemia; CSA—cyclosporine; CYP—cytochrome P450; DS—double strength; G-CSF—granulocyte–colony-stimulating factor; GM-CSF—granulocyte macrophage–colony-stimulating factor; IM—intramuscular; QD—every day; QID—four times daily; TID—three times daily; TW—three times per week; TMP/SMX—trimethoprim-sulfamethoxazole |

*Associated with use of rituximab therapy*

**Note.** Based on information from Cornely et al., 2003; Hopfer Deglin & Hazard Vallerand, 2007; Keating et al., 2004; Sandherr et al., 2006; Sudhoff et al., 1997; Thursky et al., 2006.
Table 2. Nursing Management of Infections and Nursing Guidelines for Prophylaxis and Anti-Infective Medication (Continued)

<table>
<thead>
<tr>
<th>INFECTIOUS ORGANISM</th>
<th>TREATMENTS</th>
<th>PROPHYLAXIS</th>
<th>TREATMENT</th>
<th>DURATION</th>
<th>POTENTIAL SIDE EFFECTS</th>
<th>NURSING INTERVENTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral, hepatitis B*</td>
<td>–</td>
<td>Lamivudine (100 mg per day)</td>
<td>–</td>
<td>Begin four weeks prior to therapy. Continue throughout chemotherapy and up to six months following therapy.</td>
<td>Nausea, vomiting, headaches, rare alopecia</td>
<td>• Monitor for signs and symptoms of pancreatitis. • Monitor liver function tests.</td>
</tr>
<tr>
<td>Fungal, Candida and Aspergillus</td>
<td>Fludarabine Cladribine Pentostatin Alemtuzumab</td>
<td>No established prophylaxis</td>
<td>Amphotericin B; amphotericin B lipid complex; liposomal amphotericin B</td>
<td>Up to six months after therapy</td>
<td>Chills, fever, headache, nausea, vomiting, electrolyte depletion, decreased renal function, anemia</td>
<td>• Monitor for hepatic toxicity, allergic reactions (e.g., Stevens-Johnson syndrome), and superinfections. • Monitor BUN, creatinine, liver function, and electrolytes. • Azole drugs may inhibit the CYP3A4 enzyme system and affect the activity of drugs metabolized by this system. • Evaluate medications, including glyburide, glipizide, CSA, phenytoin, benzodiazepines, and antidepressants.</td>
</tr>
<tr>
<td>Fungal, Pneumocystis jiroveci (formerly P. carinii)</td>
<td>Fludarabine with or without corticosteroids Cladribine Pentostatin Alemtuzumab</td>
<td>TMP/SMX, DS, TIW; alternatives: oral dapsone (100 mg five days per week) or nebulized pentamidine (300 mg per month) or oral atovaquone (750 mg BID)</td>
<td>–</td>
<td>Begin at start of therapy and continue 6–12 months after therapy or until CD4 counts &gt; 250,000 cells/ml.</td>
<td>Nausea, vomiting, anorexia, allergic reactions including anaphylaxis, leukopenia; hypotension, rash, decreased renal function</td>
<td>• Check for sulfa allergies. • Report signs and symptoms of reaction (e.g., rash). • Report signs and symptoms of bleeding. • Monitor vitals frequently during treatment. • Monitor for signs and symptoms of hypoglycemia.</td>
</tr>
<tr>
<td>Fungal, Listeria monocytogenes</td>
<td>Fludarabine Cladribine Pentostatin Alemtuzumab</td>
<td>Trimethoprim-sulfamethoxazole, DS, TIW</td>
<td>Ampicillin 1–3 g IV every three or four hours or gentamicin 3–5 mg/kg per day IV/IM every eight hours</td>
<td>–</td>
<td>Nausea, vomiting, diarrhea, allergy with potential for anaphylaxis, decreased renal function</td>
<td>• Ototoxicity can occur with IV dosing; monitor frequently for signs and symptoms. • Monitor BUN and creatinine for nephrotoxicity.</td>
</tr>
<tr>
<td>Vaccination</td>
<td>Influenza Pneumococcal pneumonia</td>
<td>–</td>
<td>Vaccinate patients in early stages of CLL with attenuated vaccines</td>
<td>Preseasonal vaccination</td>
<td>Injection site inflammatory reaction, mild fever</td>
<td>–</td>
</tr>
</tbody>
</table>

BID—two times per day; BUN—blood urea nitrogen; CLL—chronic lymphocytic leukemia; CSA—cyclosporine; CYP—cytochrome P450; DS—double strength; G-CSF—granulocyte–colony-stimulating factor; GM-CSF—granulocyte macrophage–colony-stimulating factor; IM—intramuscular; QD—every day; QID—four times daily; TID—three times daily; TIW—three times per week; TMP/SMX—trimethoprim-sulfamethoxazole

* Associated with use of rituximab therapy

Note: Based on information from Cornely et al., 2003; Hopfer Deglin & Hazard Vallerand, 2007; Keating et al., 2004; Sandherr et al., 2006; Sudhoff et al., 1997; Thursky et al., 2006.
B: therefore, amphotericin B remains the drug of choice for presumed invasive fungal infections in patients with febrile neutropenia (Pappas et al., 2004). Azole drugs may alter the serum levels of other medications. Nurses should pay careful attention to concomitant medications and the potential for drug interactions (Blash, 2002).

Fludarabine-Based Chemotherapy

Among the purine analogs, fludarabine frequently is incorporated as part of the backbone of CLL therapy. The incidence and spectrum of infectious complications, however, appear to be similar among the purine analogs (Ravandi & O’Brien, 2006; Wadhwa & Morrison, 2006). Treatment with fludarabine is associated with bacterial and viral infections, opportunistic infections caused by *Listeria, P. jiroveci, Mycobacterium*, and herpes viruses such as VZV. The addition of corticosteroids to fludarabine may increase the incidence of opportunistic infections with *Listeria* and *P. jiroveci* (Anaissie et al., 1998). Frontline combination therapy with fludarabine and chlorambucil may be associated with a higher incidence of infections compared with either agent administered alone, with increased incidence of fungal infections caused by *Candida* and viral infections caused by VZV or HSV (Morrison et al., 2001). The combination of fludarabine with a different alkyating agent, cyclophosphamide (FC therapy), in the frontline setting appears to have led to an incidence and spectrum of infections similar to those of single-agent fludarabine (Eichhorst et al., 2006). In patients with previously treated disease, however, FC therapy may be associated with a higher incidence of major infection compared with fludarabine monotherapy, particularly in patients with fludarabine-refractory disease (O’Brien et al., 2001; Ravandi & O’Brien, 2006). Routine anti-infective prophylaxis against bacterial or fungal infection generally is not warranted in patients receiving frontline treatment with fludarabine-based chemotherapy, although antiviral prophylaxis is recommended.

Therapy With Monoclonal Antibodies

Treatment with rituximab leads to a profound depletion of circulating B cells but does not affect the T cell–mediated immune system. In some patients, administration of rituximab may result in a decrease in immunoglobulin levels (McLaughlin et al., 1998; Ravandi & O’Brien, 2006). Infectious events and myelosuppression are not common with single-agent rituximab (Hainsworth et al., 2003; Ravandi & O’Brien); therefore, anti-infective prophylaxis typically is not required with rituximab monotherapy. Patients should be monitored, however, for the appearance of other, less common opportunistic viral infections, such as parvovirus B19 (Sandherr et al., 2006).

Treatment with alemtuzumab results in rapid depletion of circulating B cells but does not affect the T cell–mediated immune system. In some patients, administration of alemtuzumab may result in a decrease in immunoglobulin levels (McLaughlin et al., 1998; Ravandi & O’Brien, 2006). Infectious events and myelosuppression are not common with single-agent rituximab (Hainsworth et al., 2003; Ravandi & O’Brien); therefore, anti-infective prophylaxis typically is not required with rituximab monotherapy. Patients should be monitored, however, for the appearance of other, less common opportunistic viral infections, such as parvovirus B19 (Sandherr et al., 2006).

Treatment with alemtuzumab results in rapid depletion of B cells and T cells and has been associated with infectious events, including opportunistic CMV, VZV, and HSV reactivation; pneumonia (including *P. jiroveci* pneumonia [PCP]; aspergillosis; candidiasis; and septicemia, particularly in the relapsed and refractory settings (Keating et al., 2002; Moreton & Hillmen, 2003). Patients may be more susceptible to infections during times of T-cell and neutrophil nadir, which typically occur two to six weeks after initiation of alemtuzumab therapy (Keating et al., 2002; Moreton et al., 2005). Current management guidelines recommend routine anti-infective prophylaxis for patients with CLL receiving alemtuzumab, specifically trimethoprim/sulfamethoxazole (TMP/SMX) for prophylaxis against PCP and farniciclovir; acyclovir, valacyclovir, or equivalent for antiviral prophylaxis. The prophylactic regimens should be continued for at least two months after the last dose of alemtuzumab therapy or until CD4 levels recover to $\geq$ 200 cells/mcl (Bayer HealthCare Pharmaceuticals Inc., 2007; Keating et al., 2004). Patients treated with alemtuzumab in the frontline setting tend to have fewer incidences of infections but still should receive anti-infective prophylaxis, as indicated earlier (Hillmen et al., 2006; Lundin et al., 2002). Reactivation of CMV is the most common opportunistic infection observed with alemtuzumab therapy, and symptomatic reactivation may occur in as many as 30% of patients (Ferrajoli et al., 2003; Nguyen et al., 2002). Although death from CMV disease (with organ involvement) is rare, nurses should monitor patients receiving alemtuzumab therapy closely for symptoms of CMV reactivation, which frequently presents as fever of unknown origin. Recent guidelines for the management of CMV reactivation with alemtuzumab therapy recommend diligent monitoring of fever of unknown origin and, if available, routine weekly monitoring for CMV using polymerase chain reaction (PCR) assays or sensitive antigenemia tests (Keating et al., 2004; O’Brien, Keating, & Mocarski, 2006). Patients who develop symptomatic reactivation should be treated promptly with IV ganciclovir or oral valganciclovir until symptoms resolve and negative PCR or antigenemia tests are obtained. In centers where routine CMV monitoring is employed, asymptomatic CMV reactivation may be treated preemptively with ganciclovir or its equivalent (Keating et al., 2004; O’Brien et al., 2006) (see Figure 3). In addition, prophylactic antiviral therapy with valganciclovir has been effective in preventing the development of symptomatic CMV reactivation (O’Brien et al., 2005).

Alemtuzumab also may be associated with significant neutropenia, although absolute neutrophil count (ANC) typically recovers during the course of therapy. Temporary interruption in alemtuzumab therapy is recommended in patients who have ANC less than 250 cells/mcl or in the event of febrile neutropenia (Keating et al., 2004). Prophylactic administration of G-CSF or GM-CSF in patients with ANC less than 500 cells/mcl may help to prevent the occurrence of severe neutropenia during continuation of alemtuzumab therapy (Keating et al., 2004), although some study results suggest that G-CSF may increase the risk of infections (Lin et al., 2005; Sudhoff et al., 1997). NCCN (2007) guidelines on the use of growth factors should be considered in such high-risk populations. Moreover, in patients at high risk for developing infectious events, nurses play a key role in educating them and their caregivers, as well as ensuring proper administration of medication, monitoring potential side effects, and assessing patient adherence (Lynn, Williams, Sickler, & Burgess, 2003; Nirenberg et al., 2006). Antifungal agents are not routinely recommended for prophylactic use because of the possibility of inducing resistant fungal strains (Keating et al., 2004).
Combination Chemoimmunotherapy

With the introduction of monoclonal antibodies in CLL therapy, combination regimens with purine analogs and rituximab or alemtuzumab are being used increasingly in an effort to improve response rates and duration. However, because the risk for severe myelosuppression may be higher with the more aggressive therapies, vigilant monitoring for infectious complications is required. Major infections (≥ grade 3) have been reported in about 20% of patients with CLL receiving frontline combination therapy with fludarabine and rituximab (FR) (Byrd et al., 2003). Common opportunistic infections with FR therapy include VZV reactivations resulting in herpes zoster, localized HSV infection, and PCP. The incidence of major infections in patients receiving frontline FCR combination therapy (FR plus cyclophosphamide) was similar to that seen with the FR regimen (Keating et al., 2005). Prophylactic use of anti-infective agents with FR therapy include VZV reactivations resulting in herpes zoster, localized HSV infection, and PCP. The incidence of major infections in patients receiving frontline FCR combination therapy (FR plus cyclophosphamide) was similar to that seen with the FR regimen (Keating et al., 2005). Prophylactic use of anti-infective agents with FR therapy may not be warranted in patients with intact immune function treated with frontline CLL therapy, although about 50% of patients in the frontline FCR study were treated with prophylactic TMP/SMX and valacyclovir (Keating et al., 2005). In patients with relapsed or refractory CLL treated with FCR therapy, major infectious events (e.g., pneumonia, sepsis, infections requiring hospitalization) were reported in only 16% of patients, likely thanks to the administration of anti-infective prophylaxis (Wierda et al., 2005).

The combination of fludarabine and alemtuzumab (FluCam) also has been evaluated in patients with relapsed or refractory CLL (Elter et al., 2005). Despite the pretreated status of the patients, major infections (grade 3 or 4) were reported in only 11% of patients receiving FluCam because of the use of anti-infective prophylaxis with TMP/SMX and valacyclovir and preemptive therapy with ganciclovir for CMV reactivation. Thus, in patients with relapsed or refractory CLL receiving chemoimmunotherapy, routine incorporation of anti-infective prophylaxis may be necessary to minimize the development of severe infectious complications.

Maintaining a Consistent Treatment Schedule While Preventing Infections

The goals of CLL therapy are to optimize response while minimizing the side effects associated with therapy, to prevent or manage infections, and to improve or maintain quality of life for patients. Nurses play a vital role in enabling patients to maintain scheduled treatment courses while ensuring overall patient health. Patients at high risk for infections require vigilant monitoring by all members of the healthcare team and caregivers. Because many CLL therapies are administered orally and minor infections also are treated with oral medications, nurses should provide patients and caregivers with clear instructions on disease and medication management to ensure successful administration of home-based therapies. Adherence to medication schedules, prompt reporting of side effects from CLL and anti-infective therapies, and real-time management of side effects will positively contribute to the overall success of CLL therapy. Factors that may influence adherence include cost of medications...
to patients, number of doses per day, dosing frequency, and side effects (Insull, 1985).

Before beginning patient education, nurses must evaluate patients’ readiness to learn, motivation, and ability to understand the information. The results of learning assessments, education topics that were covered, and outcomes of education should be documented in patients’ records. Nurses should conduct patient and caregiver education in face-to-face sessions at the beginning of therapy and at periodic intervals throughout treatment, as needed. Nurses also should provide counseling when anti-infectives are prescribed, whether prophylactic or for treatment of active infections. Frequent telephone contact should be encouraged, especially for patients who live a considerable distance from a treatment center. Nurses should encourage patients and caregivers to keep a diary of medications and symptoms and to immediately contact a nurse if they develop a high temperature (≥ 100.5°F or 38°C), cough, sore throat, or an abnormal wound (slow in healing, swollen, or hot to the touch) (Lynn et al., 2005).

Case Study

M.G., a 68-year-old woman, was diagnosed two years ago with Rai stage III/Binet stage C CLL. Prior therapy included chlorambucil (an alkylating agent) and fludarabine (a nucleoside analog). Her disease progressed on fludarabine therapy, and she was started on alemtuzumab monotherapy four weeks ago. She has been tolerating therapy well. Early this morning, M.G. called the answering service before the clinic opened to report a fever of 100.5°F or 38°C.

The nurse immediately returns the call for more information. The patient states that she has no associated symptoms, other than a dry cough that started during the night. She has not taken any medication for her fever or cough. She has been taking TMP/SMX double strength two times per day (BID) three times weekly and famciclovir BID for prophylaxis and states that she has taken all doses of both medications as ordered. The nurse instructs M.G. to come to the clinic. When she arrives, she is seen by the advanced practice nurse (APN) for an examination. She is found to be febrile (101.5°F or 38.6°C), with an intermittent dry cough but no other signs or symptoms of infection. Aerobic and anaerobic blood cultures are drawn; a urine specimen shows no elevation in leukocyte esterase but is sent to microbiology for analysis. Prior to alemtuzumab therapy, her baseline quantitative CMV was less than 15 CMV DNA copies/ml (negative). Quantitative CMV PCR assays have been drawn weekly during therapy to monitor for CMV reactivation; serial results have remained negative (< 15 CMV DNA copies/ml). Blood now is drawn for a quantitative CMV PCR assay; the results will be available within 24 hours. CBC performed when M.G. arrived at the clinic was normal, except for white blood cell count 11,000/mcl and ANC 600/mcl. CD4+ T-cell count is 180/mcl. Chest radiograph reveals no infiltrates, consolidation, or effusions. Differential diagnoses include CMV reactivation, pneumonia, PCP, aspergillosis, and viral upper-respiratory infection.

M.G. is due to receive alemtuzumab treatment tomorrow. To this point, she has had a good response to alemtuzumab, with a reduction in marrow infiltration to 25%. The differential diagnosis most directly related to alemtuzumab therapy and the one that should be treated empirically immediately is CMV reactivation. M.G. is started on oral valganciclovir and a broad-spectrum antibiotic, levofloxacin (Levaquin®, OrthoMcNeil Pharmaceutical), and the nurse educates her on the administration schedule and the potential side effects. The nurse sends M.G. home with instructions to monitor her temperature every four hours at home, keep a chart of her temperature, and return to the clinic the following morning.

The following morning, M.G. returns to the clinic. Her examination findings are essentially unchanged, with no new symptoms. The intermittent dry cough continues. Quantitative PCR assay results indicate CMV reactivation at a value of more than 100 CMV DNA copies/ml (high positive), and she remains febrile, although her temperature has decreased slightly to 100.2°F or 37.8°C. The oncologist and APN are consulted, and the team decides to hold alemtuzumab and treat the patient with IV ganciclovir. M.G. is admitted to the day hospital to begin IV ganciclovir therapy, with plans to continue her parenteral antiviral therapy with a home infusion service. Antiviral CMV therapy continues for a week, with quantitative PCR assay monitoring every two days. On the second day of ganciclovir therapy, the quantitative CMV PCR decreases to 20 copies/ml of CMV DNA, which is only slightly above the low-positive threshold. Levofloxacin is continued for a total of 10 days. After one week of ganciclovir and antibiotic therapy, her fever and dry cough resolve and quantitative CMV PCR returns to negative. Alemtuzumab (with prophylactic TMP/SMX and oral valganciclovir) is restarted, and weekly quantitative PCR monitoring continues. Before sending M.G. home, the nurse provides counseling to reinforce the importance of maintaining the dosing schedule for the prophylactic anti-infective treatments, encourages M.G. to keep a diary of medications and symptoms, and instructs her to promptly report any signs or symptoms of infections (e.g., fever, cough).

Summary

With the availability of newer therapeutic regimens for CLL, greater emphasis is needed on the supportive care of patients with CLL to reduce infection-related morbidity and mortality. Patients with CLL are at risk for a broad spectrum of infectious complications, ranging from reactivation of dormant endogenous viruses to life-threatening fungal and bacterial infections. Such infections can be life threatening but can be managed by ensuring patient adherence to recommended prophylactic anti-infective regimens, early reporting of potential signs and symptoms of infections, and aggressive management of active infections. Infection management is best facilitated by oncology nurses who understand and can clearly communicate the CLL disease process, effects of CLL therapies on the immune system, and recommended anti-infective agents and their side effects. Nursing guidelines for the management of infections in patients with CLL should incorporate diligent monitoring techniques and anti-infective prophylaxis measures, particularly when patients are considered to be at high risk for infectious events. Empiric treatment of suspected infections must be considered to prevent progression of infections. Prompt treatment of active infections is mandatory in all patients with CLL, regardless of therapy, because of the inher-
ent immune dysfunction that is a characteristic feature of the disease. Evidence-based guidelines are available for management of potential or confirmed infections in patients with CLL and should be used by all levels of healthcare providers to improve outcomes for patients with CLL.

Author Contact: Mollie Moran, MSN, CNP, can be reached at mollie.moran@osumc.edu, with copy to editor at CJONEditor@ons.org.

References


