FEATURE ARTICLE

Emerging Therapeutic Options for B-Cell Disorders: Idiopathic Thrombocytopenic Purpura and Chronic Lymphocytic Leukemia

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B-cell disorders include a large group of malignant and nonmalignant diseases with tremendous variation in incidence, natural history, treatment, and prognosis. This article will focus on adult idiopathic thrombocytopenic purpura (ITP) and chronic lymphocytic leukemia (CLL). Clinicians must individualize treatment for ITP and CLL to each patient. Observation without intervention is appropriate for some patients, whereas immediate treatment is indicated for others. Deciding when to treat and which agents to use can be difficult, but new therapeutic options are emerging for both conditions.

At a Glance

✦ Treatment options for idiopathic thrombocytopenic purpura (ITP) and chronic lymphocytic leukemia (CLL), both B-cell disorders, are complex.
✦ New treatments for ITP and CLL include monoclonal antibodies and combination chemotherapy regimens.
✦ Oncology nurses need information about disease etiology, diagnosis, staging, treatment options, and nursing management strategies.

Idiopathic Thrombocytopenic Purpura

Definition and Etiology

ITP is an autoimmune disorder characterized by autoantibody binding to platelet antigens. The binding induces premature destruction of platelets, particularly by the spleen but also by other components of the reticuloendothelial system, which is composed primarily of blood monocytes and tissue macrophages, resulting in thrombocytopenia (British Society for Haematology, 2003; Crow, Song, Siragam, & Lazarus, 2006; George et al., 1996).

ITP is defined as isolated thrombocytopenia without other significant abnormalities on complete blood count or peripheral blood smear. It can be a primary or secondary disorder. The etiology of primary ITP is unknown; however, secondary ITP is associated with certain medications, infections, other autoimmune diseases, transfusions, or pregnancy. The most common diagnosis of secondary ITP in malignant disease is in patients with CLL (British Society for Haematology, 2003; George et al., 1996). This article will focus on adult primary ITP.

Prevalence and Natural History

In adults, ITP typically is an insidious and chronic process with presenting symptoms correlating to the degree of thrombocytopenia, ranging from an incidental diagnosis without symptoms to life-threatening bleeding. In children, the disease usually is acute in onset and spontaneously resolves (British Society for Haematology, 2003; George et al., 1996).

Estimates of incidence suggest that ITP occurs in 1–13 adults and children per every 100,000 people (Sandler, Schexneider, ...
Presentation

The typical presentation of patients with ITP depends largely on the platelet count at diagnosis. A normal platelet value generally is considered to range from 150,000–350,000/mm³ (Cines & Bussel, 2005). Patients with platelet values of 50 x 10⁹/L or more often are diagnosed incidentally and have no clinical evidence of thrombocytopenia. Those with platelet values from 30,000–50,000/mm³ may note easy bruising (Cines & Bussel; Sandler et al.). Patients with platelet values below 20,000/mm³ may present with mucosal bleeding, including petechiae, purpura, menorrhagia, epistaxis, gingival bleeding, or hematuria (Cines & Bussel; Sandler et al.). Patients rarely present initially with melena, massive internal bleeding, or intracranial hemorrhage. Most patients are in their usual state of health with the exception of possible mild fatigue (Hoffman et al., 2005).

Differential Diagnosis and Workup

Although ITP is the most common cause of significant thrombocytopenia in healthy young adults, it is a diagnosis of exclusion (British Society for Haematology, 2003; George et al., 1996; Hoffman et al., 2005; Kuwana et al., 2005). An initial workup should include a detailed history and physical examination. The patient’s history can reveal the duration, extent, and severity of bleeding and permit assessment of other medical conditions or medications associated with ITP or thrombocytopenia. Physical examination offers additional information about the extent and severity of bleeding and can uncover the presence of previously unrecognized medical conditions associated with ITP or thrombocytopenia. Fewer than 3% of adults with ITP have splenomegaly on examination (Cines & Bussel, 2005; Sandler et al., 2006). If splenomegaly is noted, other causes of thrombocytopenia should be strongly suspected.

A complete blood count and examination of a peripheral blood smear are included in the initial workup. Apart from a low platelet count, individuals with ITP are likely to have a normal complete blood count. The peripheral blood smear is examined to rule out leukemias as well as other hematologic disorders, including myelodysplasia and various anemias. Additional testing may include HIV and hepatitis C screening, an autoimmune profile or screen, thyroid function studies, bone marrow examination, various imaging studies, and platelet and antiplatelet antibodies to eliminate other potential causes of thrombocytopenia. Helicobacter (H.) pylori screening could be considered, but infection with H. pylori is rare in patients with ITP (British Society for Haematology, 2003; Cines & Bussel, 2005; Fabris et al., 2005; George et al., 1996; Hoffman et al., 2005; Suvajdzic et al., 2006). Although about 75% of pregnant women demonstrate thrombocytopenia, ITP in pregnancy is rare. No additional studies are recommended to diagnose ITP in pregnancy (George et al., 1996).

Healthy individuals frequently are diagnosed with borderline thrombocytopenia (i.e., platelet values from 100,000–150,000/mm³) during routine examination (Cines & Bussel, 2005). One long-term follow-up study of such patients showed that 64% had stable persistent thrombocytopenia or spontaneous resolution. Only about 7% developed ITP, and 12% developed other autoimmune disorders. Women accounted for 85% of patients diagnosed with other autoimmune disorders (Stasi, Amadori, Osborn, Newland, & Provan, 2006).

Treatment

Because few large, randomized trials have been conducted among patients with ITP, treatment must be individualized. Observation without intervention usually is appropriate for patients with platelet counts of 50,000/mm³ or greater who are not bleeding and not at high risk for bleeding. Treatment is indicated when platelets range from 20,000–30,000/mm³ or are less than 50,000/mm³ with bleeding or high-risk status (British Society for Haematology, 2003; Cines & Bussel, 2005; George et al., 1996; Hoffman et al., 2005).

Corticosteroids: Steroids are considered first-line therapy, with responses in 66%–75% of adult patients (Cines & Bussel, 2005). Oral prednisone is the outpatient drug of choice, with a starting dose of 1 mg/kg daily for two to four weeks. For responders, after the initial two to four weeks, prednisone should be tapered gradually over several weeks. Patients initially responsive to steroids often experience worsening thrombocytopenia during oral steroid tapers and may require increased doses of prednisone to maintain adequate platelet counts. In patients who have repeated episodes of thrombocytopenia during steroid tapers, the addition of IV immunoglobulin (IVIG) or splenectomy should be considered (British Society for Haematology, 2003; George et al., 1996; Vianelli et al., 2005). Although initial response rates vary from 50%–90%, long-term responses can be expected in only 10%–33% of initial responders (British Society for Haematology; Cines & Bussel).

IV immunoglobulin: IVIG is considered a first-line therapy for ITP and can be given alone or with steroids. IVIG is manufactured from pooled human immunoglobulin. Although the mechanism of action is not well understood, IVIG is believed to be active in ITP by blocking autoantibody binding to platelets and interrupting several other potential immune system responses contributing to autoimmunity (Cines & Bussel, 2005; Crow et al., 2006).

Commonly recommended IVIG doses are 0.4 g/kg daily for five days or 1 g/kg as a single dose (Cines & Bussel, 2005). As many as 75% of patients with ITP respond to IVIG (British Society for Haematology, 2003; George et al., 1996). Unfortunately,
responses are short, generally lasting three to four weeks, with platelet values returning to pre-IVIG ranges. Short responses prompt the use of maintenance IVIG either monthly or as thrombocytopenia worsens (British Society for Haematology; George et al., 1996). In patients with ITP not yet requiring treatment, IVIG can be used very effectively to temporarily increase platelet values for surgery, childbirth, or other planned invasive procedures (British Society for Haematology).

**Anti-Rh(D):** Anti-Rh(D) is an immunoglobulin commonly administered to Rh(D)-negative women potentially carrying an Rh(D)-positive fetus. Anti-Rh(D) at 50–75 mcg/kg IV has been shown to increase platelet counts in as many as 90% of Rh(D)-positive non-splenectomized patients with ITP (Hoffman et al., 2005; Ramadan & El-Agnaf, 2006). The reticuloendothelial system, especially the spleen, is believed to destroy Rh(D)-positive red blood cells, thus sparing autoantibody-coated platelets. IV anti-Rh(D) is administered as needed to stabilize or increase platelet values. Once stabilization or improvement has occurred, treatment generally is discontinued (British Society for Haematology, 2003; Hoffman et al.; Stasi & Provan, 2004; Trivedi & Bussell, 2005).

**Splenectomy:** Prior to the introduction of steroids in the 1950s, splenectomy was a treatment option for patients with ITP that lengthened the survival of antibody-coated platelets. The procedure is not technically curative because antibody coating still occurs. Removing the spleen eliminates the major source of destruction of the antibody-coated platelets and can be clinically curative (British Society for Haematology, 2003).

Splenectomy now is reserved generally as a second-line treatment option, although it is used in first-line emergent situations (Cines & Bussell, 2005). Positive response to splenectomy most often is defined as the presence of a postoperative platelet count of 50,000/mm³ without maintenance therapy (British Society for Haematology, 2003; George et al., 1996; Hoffman et al., 2005). In analyses of data sets from large, retrospective trials, approximately two-thirds of patients demonstrate normalization of platelet counts following splenectomy (Kahn & McCray, 2004; Kojouri, Vesely, Terrell, & George, 2004; Vianelli et al., 2005). Responses often are sustained with no additional therapy required (British Society for Haematology; George et al., 1996; Hoffman et al.).

For patients who do not achieve a complete response, some improvement in platelet values can be expected (British Society for Haematology, 2003; Johansson et al., 2005). Eighty-five percent of patients undergoing splenectomy can expect a stable hemostatic response, with a 5- to 10-year relapse rate of about 25% in responding patients (Johansson et al.; Kojouri et al., 2004).

To date, researchers have not developed any successful models for predicting who will benefit from splenectomy, duration of response, or frequency of surgical complications (British Society for Haematology, 2003; Kojouri et al., 2004). Patients completely refractory to prior therapies have been found to have less favorable responses to splenectomy (British Society for Haematology; Hoffman et al., 2005). Multiple retrospective data analyses have reported that responsiveness to steroids and IVIG, in particular, is a predictor of positive response after splenectomy (British Society for Haematology). Other researchers have reported that higher platelet values after splenectomy correlate with more favorable responses (Vianelli et al., 2005). In addition, indium-labeled autologous platelet scanning has been used to determine the extent of platelet destruction in the spleen, with higher splenic destruction associated with favorable responses after splenectomy (British Society for Haematology).

Approximately 1% of patients undergoing splenectomy develop bacterial sepsis, which is the major risk of the procedure. The benefit of short- and long-term prophylactic antibiotics after splenectomy to reduce pneumococcal infection is not clear (British Society for Haematology, 2003; Hoffman et al., 2005). Many clinicians immunize candidates for splenectomy against pneumonia, influenza, and meningitis (Cines & Bussel, 2005), and all patients require careful, lifelong monitoring for the development of infection. Unfortunately, no large data sets are available on the progress or survival of patients with ITP who are unresponsive to splenectomy (McMillan & Durette, 2004).

**Monoclonal antibodies:** Rituximab (Rituxan®, Genentech, Inc., South San Francisco, CA), a chimeric anti-CD20 monoclonal antibody, appears to be a promising agent for treating ITP in the second or third line. Rituximab depletes B cells, and researchers believe that the removal of the memory B-cell compartment causes a decrease in autoantibody formation (Koene, 2006). Several clinical trials have demonstrated response rates of about 55% (Cooper et al., 2004; Giagounidis et al., 2002; Stasi, Pagano, Stipa, & Amadori, 2001), and patients who achieve complete remission often experience long response durations (i.e., as long as four years) (Cooper et al.). Some studies and retrospective analyses suggest better response rates in patients who are young, are pretreated less heavily, or have shorter duration of disease (Arnold et al., 2005; Braendstrup et al., 2005; British Society for Haematology, 2003; Case, Hedlund, Ebrahim, & Boyd, 2005; Garcia-Chavez, Vela-Ojeda, Gonzalez-Acosta, & Ovilia-Martinez, 2005; Penalver et al., 2006). Many clinicians have incorporated rituximab into their ITP treatment armamentarium, although the U.S. Food and Drug Administration (FDA) has not approved the drug for that indication. Cines and Bussel (2005) used rituximab in patients for whom splenectomy had failed at a dose of 375 mg/m² IV weekly for four weeks. Side effects of rituximab usually are related to the first infusion (i.e., infusion reaction). Optimal dosing, schedules, and use with other agents remain under investigation. Alemtuzumab (Campath®, Berlex, Wayne, NJ), a humanized anti-CD52 monoclonal antibody, has shown activity in patients with chronic ITP but has not been studied extensively (British Society for Haematology; Stasi & Provan, 2004) and is not in wide clinical use for this condition.

**Other agents and approaches in treatment-refractory patients:** Physicians use other regimens and approaches in patients who are refractory to corticosteroids, immunoglobulins, rituximab, and splenectomy. Danazol, an attenuated androgen, can be combined effectively with other agents, especially immunosuppressants, to achieve responses (Cines & Bussel, 2005). Danazol appears to impair the clearance of immunoglobulin-coated platelets and reduce antibody production. It has increased platelet counts by 40%–50%, particularly in postmenopausal women. Patients should take the agent for four to six months to achieve maximum benefit (Cines & Bussel; Sandler et al., 2006). Danazol’s adverse events include mood
changes, menstrual disorders, hirsutism, rash, myalgias, and transaminase elevations. The androgen often is administered with corticosteroids and IVIG; on response, the agents can be stopped (Cines & Bussel, 2005). A standard dose of danazol is 1 g/kg IV weekly for three to four weeks. In combination with an immunosuppressant, the dose is 10–15 mg/kg per day (Sandler et al.).

A preferred immunosuppressant is azathioprine, an antimetabolite often combined with danazol and prednisone to achieve response and permit dose reduction of prednisone. Administered at 2 mg/kg per day orally or via IV, azathioprine has a better adverse event profile than other immunosuppressants such as cyclophosphamide and cyclosporine. It has a sustained response rate of 20%–40% (Cines & Bussel, 2005). Azathioprine produces responses slowly; therefore, administration should continue for at least 12 months and be discontinued gradually. Another immunosuppressant, mycophenolate mofetil (MMF), Cellcept®, Roche, Nutley, NJ) has demonstrated a beneficial effect in patients with chronic ITP (Zhang et al., 2005). MMF also is administered with danazol; patients receive 500 mg orally twice per day with increasing doses (1,000–1,500 mg) after two weeks (Cines & Bussel). Similar to azathioprine, on response, MMF can be tapered gradually but rarely is discontinued completely (Cines & Bussel). In one study, 15 of 23 patients demonstrated responses as long as 39 months with minimal toxicity (Howard, Hoffbrand, Prentice, & Mehta, 2002).

Patients with refractory ITP sometimes receive other regimens that often are less effective than the agents described previously and may carry more severe toxicities. For example, dapsone, an antibacterial sulfone with immunosuppressive effects at 75–100 mg orally per day can produce results similar to danazol but should be avoided in patients with glucose-6-phosphate dehydrogenase deficiency (Cines & Bussel, 2005). Cyclophosphamide is administered orally (1–2 mg/kg daily) or via IV (two to three cycles at 500–1,000 mg/m² every three to four weeks). Although responses may appear within three months, thrombocytopenia may worsen and neupotropenia may develop. Vinca alkaloids also have been used in patients with refractory ITP, but transient responses and a high risk of neuropathy have been reported. Administered weekly for four to six weeks, vinca alkaloids have demonstrated improvements in platelet counts for as long as three weeks, with an approximately 50% response rate in patients who have undergone splenectomy. However, patients have shown a sustained response rate of less than 10% (British Society for Haematology, 2003). Cyclophosphamide has been used with modest success, but thrombocytopenia and neutropenia may worsen. Patients receiving cyclophosphamide may require support with growth factors and prophylactic antibiotics (Cines & Bussel). Finally, interferon-alfa (Roferon®, Roche) has demonstrated a response rate of about 25%, but it also may exacerbate ITP and has not shown consistent benefit (British Society for Haematology).

Emergency care and platelet transfusions: Physicians should consider hospitalization for patients presenting with platelet values 20,000/mm² or less or those initially or at relapse (Cines & Bussel, 2005). A full evaluation can be completed in a more timely fashion in a hospital than in the outpatient setting. During inpatient hospitalization, response to treatment can be documented and emergency measures can be instituted as appropriate. Full supportive care often includes bleeding precautions, discontinuation or minimization of drugs that interfere with platelet function, blood pressure monitoring and control, trauma reduction, and medication administration (e.g., aspirin).

Intravenous immunoglobulin (IVIG) has demonstrated a response rate of about 25%, but it also may exacerbate ITP and has not shown consistent benefit. AMG 531, however, binds to the TPO receptor and has a low potential to elicit antibodies that cross-react to endogenous TPO, minimizing its potential to cause adverse reactions and maximizing its efficacy (Nichol, 2006).

The most recent clinical trial reports on AMG 531 indicate that it increases platelet counts in patients with chronic ITP, causes few serious adverse events, and enhances patients’ quality of life. Kuter et al. (2006) provided updated efficacy and safety data from their continuing trial of long-term dosing of AMG 531 in December 2006. The trial is an open-label extension of previous phase II and phase III trials. One hundred four patients were enrolled and received a basic dose of 1 mcg/kg by subcutaneous injection weekly, which is adjustable to 15 mcg/kg depending on the platelet response or the dose received in the previous study. Upon response, patients could self-administer their injections. The interim safety analysis included 36 patients previously enrolled in a phase II trial. Of those, 30 (83%) have had a splenectomy and 12 began the study using corticosteroids. The most frequent adverse events were headache, upper respiratory infection, and fatigue. Only four patients experienced serious adverse events, and two patients withdrew from treatment. No neutralizing antibodies were detected. The efficacy subset included 27 patients who received at least 48 weeks of therapy. The mean platelet count and mean dose of AMG 531 remained stable from weeks 24–48. The mean platelet count was 100,000/mm³ during weeks 1–24 and 131,000/mm³ during weeks 25–48. Six of 12 patients were able to discontinue corticosteroids, and two experienced greater than a 25% dose reduction. Kuter et al. concluded that AMG...
531 in individualized weekly doses permits patients to maintain safe platelet counts and decrease or discontinue corticosteroids with minimal adverse events. In a companion report, George et al. (2006) reported that patients in their study also experienced improved quality of life in dimensions such as fatigue, other symptoms, and the ability to work.

Rituximab remains another focus of investigation. Although it has demonstrated efficacy and safety in relapsed or refractory ITP and is used widely, the FDA has not approved it for this indication. A meta-analysis reported in December 2006 confirmed that rituximab produces objective responses in 55% of patients and that retreatment produces similar results. Rituximab causes minimal toxicity, but its results match those of immunosuppressants. The researchers called for prospective clinical trials to validate their findings and identify patient characteristics that would predict response to rituximab (Ramanarayanan, Brodzik, Czuczzman, & Hernandez-Illizaliturri, 2006).

Other clinical trials in ITP are developing laboratory studies that can be used to more accurately diagnose the condition and monitor and recognize responses to therapy. For example, Cho, Lee, Kim, Lee, and Choi (2006) described a diagnostic method that uses immature platelet fraction. They established a reference range in healthy individuals (0.4%-5.4%), with much higher values for patients with ITP. Cho et al. argued that a rapid, inexpensive, and automated method for measuring immature platelet fraction is feasible. Another research group has demonstrated that immature platelet fraction measurements describe response to treatment and may provide insights into the mechanisms of action of effective agents (Psaila, Villarica, Czuczeman, & Hernandez-Ilizaliturri, 2006).

A significant area of study is prediction and prognosis in ITP. In one study, patients who had ADAMTS 13 deficiencies at the time of diagnosis had a higher risk of relapse than those who had normal ADAMTS 13 (i.e., a Zn-dependent metalloproteinase produced in the liver). A deficiency of the enzyme is associated with thrombotic thrombocytopenic purpura, and a relationship with ITP has been established (Scull, Starke, Mackie, & Machin, 2006). Patients with ITP uniformly expressed antibodies to ADAMTS 13. In addition, treatment with rituximab appeared to normalize ADAMTS 13 in a substantial proportion of treated patients (Scull et al.). Effective methods of predicting disease course and response to treatment may greatly enhance outcomes for patients with ITP.

**Nursing Implications**

Nurses play a significant role in the care of adult patients with ITP, in whom the likelihood of chronic disease is extremely high. Patient and caregiver education is critical regarding the disease itself, the wide variety of treatment options, and appropriate lifestyle modifications. Signs and symptoms of bleeding require intense review with patients and caregivers. Patients and caregivers must understand how to separate the signs and symptoms of minor bleeding (e.g., petechiae, gingival bleeding, easy bruising) that may be reported to the appropriate providers by telephone from those of potentially life-threatening bleeding (e.g., black, tarry stools; hematemesis; changes in mental status) that should prompt immediate emergency department assessment.

Patients with ITP require education on avoiding activities that may result in injury and falls: contact sports, high-impact physical activities, or pursuits and hobbies that are likely to result in breaks in the skin, such as woodworking or carpentry. Those with unstable gait or at risk for falls need in-depth assessments and appropriate interventions, which may include home environment assessments and training on the use of balance-assisting devices, such as canes and walkers. Patients should receive education about bleeding precautions and possible lifestyle changes, including using electric shavers and soft toothbrushes as well as avoiding flossing the teeth at times of severe thrombocytopenia.

Nurses should stress the importance of avoiding medications, such as aspirin or ibuprofen, that may increase platelet destruction and are found in many over-the-counter preparations. Other common platelet-decreasing medications are barbiturates, digoxin, gold salts, H2 blockers, heparin, methyldopa, penicillin, procainamide, quinidine, quinine, sulfonamides, and valproic acid. When clinicians consider changing medications in patients with ITP, they must assess the potential impact on platelets. The use of herbal products also requires close assessment and research of any potential impact on platelet values or coagulation. Depending on the degree of thrombocytopenia, the use of acupuncture or intramuscular injections may be contraindicated.

Most patients with ITP receive one or more courses of immunosuppressive agents (with or without splenectomy); therefore, they must receive education about the signs and symptoms of infectious complications. Patients also should be aware that they may not present with typical signs and symptoms of infection and should seek medical attention for any general decline in their overall physical well-being. Nurses should educate patients about the importance of identifying their postsplenectomy status, such as by wearing a MedicAlert® (MedicAlert Foundation International, Turlock, CA) bracelet, to alert emergency providers of their important medical history.

Clinicians should frequently assess complications, including osteoporosis and avascular necrosis, in patients on long-term steroids. Bisphosphonates or hormonal replacement therapy may be indicated. Patients should receive additional therapy-specific education as needed, especially for chemotherapeutic agents and monoclonal antibodies. Patients who do not have cancer but are receiving the agents may require additional education regarding the reasons the agents are appropriate for nonmalignant diseases (Baldwin, 2003).

**B-Cell Chronic Lymphocytic Leukemia**

**Definition and Etiology**

CLL is a malignant low-grade disorder arising from mature B cells. The disease has tremendous variations, ranging from very indolent to rapidly progressing states (Abbott, 2006; Wierda, 2006). Approximately 30% of patients will have a “typical” course of CLL with relatively indolent disease, 10-year survival, and eventual death that may be unrelated to CLL. Some will have an aggressive course of disease with death in two to three years. Others may have an initially indolent course for three years or
more, followed by rapid disease progression and a one- to two-year end stage, when the disease and complications of therapy account for significant morbidity (Abbott).

Most patients receive a diagnosis of CLL at 65–70 years of age. The ratio of males to females is 1.5:1, with a higher incidence in Caucasians of both genders (American Cancer Society, 2006b; Rai et al., 2004). In the United States, approximately 10,000 people per year are diagnosed with CLL (American Cancer Society, 2006a). Overall survival after diagnosis is 48.2% at 5 years and 22.5% at 10 years (Lin et al., 2004). For most patients, the etiology of CLL is unknown. Only 5%–10% of patients have an inherited susceptibility to CLL (Catovsky, 2004).

Presentation

Approximately 25% of patients with CLL are completely asymptomatic at the time of diagnosis. Most asymptomatic patients have a diagnostic workup based on abnormal routine complete blood count results. About 5%–10% have typical B symptoms, including fever greater than 100.5°F for more than two weeks without infection, unintentional weight loss of 10% or more of body weight in the previous six months, night sweats without infection, and extreme fatigue (Abbott, 2006).

Many patients diagnosed with CLL initiate contact with their healthcare providers because of painless lymph node swelling, often in the cervical area. They usually describe spontaneously waxing and waning lymphadenopathy, without complete disappearance. Common physical findings include lymphadenopathy (87%), splenomegaly (54%), and hepatomegaly (14%) (Abbott, 2006; Rai et al., 2004).

Diagnosis, Staging, and Prognosis

In addition to a detailed history and physical examination, a full diagnostic workup may include a complete blood count with differential, lactic dehydrogenase levels, peripheral blood smear, beta-2 microglobulin levels, bone marrow aspirate and biopsy, immunophenotyping, cytofluorimetry in situ hybridization on peripheral blood or bone marrow, x-rays or computed tomography scans, and lymph node biopsy (Abbott, 2006; National Comprehensive Cancer Network [NCCN], 2006; Rai et al., 2004). The diagnosis of CLL requires all of the following: (a) lymphocytosis more than 5,000/mm³ for more than two months, (b) bone marrow involvement of more than 30% lymphocytes, and (c) clonal lymphocytes (derived from a single cell line). Immunophenotyping most often reveals CD5+, CD19+, CD23+, CD20 weak or positive, cyclin D1-negative, and CD22 weak or negative (Abbott; Rai et al., 2004), which are characteristic B-cell surface marker proteins. Cytofluorimetry may reveal various abnormalities such as gene deletions and zeta-associated protein 70 (ZAP-70) status that may be useful in determining prognosis (NCCN).

In the United States, the Rai Staging System typically is used for staging CLL, although it is not the only recognized staging system. The modified Rai system ratings can guide initiation of treatment and provide accurate prognostic information (NCCN, 2006; Rai et al., 1975). In Europe, the Binet Classification System is used, but it does not include risk status (Binet et al., 1981). See Table 1 for the progressive stages of each system.

Table 1. Chronic Lymphocytic Leukemia Classification Systems

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<th>STAGE</th>
<th>DESCRIPTION</th>
<th>RISK STATUS</th>
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<tr>
<td>0</td>
<td>Lymphocytosis, absolute lymphocytes &gt; 5,000/mcl, and &gt; 40% lymphocytes in bone marrow</td>
<td>Good</td>
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<tr>
<td>I</td>
<td>Stage 0 with enlarged node(s)</td>
<td>Intermediate</td>
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<tr>
<td>II</td>
<td>Stage 0–I with splenomegaly, hepatomegaly, or both</td>
<td>Intermediate</td>
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<tr>
<td>III</td>
<td>Stage 0–II with hemoglobin &lt; 11.0 g/dl</td>
<td>High</td>
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<tr>
<td>IV</td>
<td>Stage 0–III with platelets &lt; 100,000/mm³</td>
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<th>BINET CLASSIFICATION SYSTEM</th>
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Note. Based on information from Binet et al., 1981; Rai et al., 1975.

Additional risk factors that indicate poor prognosis have been identified.

- Lymphocyte count doubling time of less than a year (aggressive disease)
- Low hemoglobin (< 11 g/dl; aggressive or advanced disease)
- Diffuse bone marrow infiltrate (aggressive disease)
- Elevated beta-2 microglobulin levels (> 2.0 mg/l; poor prognosis); beta-2 microglobulin is a measure of tumor burden.
- CD38 expression in more than 20% of cells (poor prognosis) (Damle et al., 1999).

Statistics indicate that 25% of Rai stage 0 patients die from CLL-related causes and more than 50% progress to aggressive disease (Ellis et al., 2005). Researchers have sought additional methods to distinguish among patients whose disease will remain indolent and those whose disease will progress. They have found that studies of cytogenetic abnormalities, immunoglobulin-variable heavy chain mutation status, and ZAP-70 status could help to make those differentiations (Ellis et al.; Strauchen, 2004).

The presence (or absence) of somatic mutations of the immunoglobulin gene is seen in the heavy chain variable (immunoglobulin VH) regions. The tyrosine kinase protein ZAP-70, which is expressed normally on T and natural killer cells, is expressed in CLL in inverse correlation to immunoglobulin VH mutation status (i.e., the less ZAP-70, the more likely the mutation). Thus, positivity for ZAP-70 can indicate that the progress of the disease is likely to be aggressive (Crespo et al., 2003; Rassenti et al., 2004; Strauchen, 2004; Wiestner et al., 2003), but negativity suggests that the disease is likely to be less aggressive.

Evidence now suggests that CLL is actually two distinct disorders. One shows a proliferation of pregerminal center B cells (not exposed to antigen) that are positive for CD38 and have no somatic
mutations of the variable region of the immunoglobulin gene. The other is a proliferation of postgerminal center memory B cells that are negative for CD38 and have somatic variations of the variable region of the immunoglobulin gene. The two illnesses progress differently. The CD38+ type progresses rapidly and aggressively, whereas the CD38– type usually has an indolent course (Ellis et al., 2005; Hamblin et al., 2002; Wiestner et al., 2003).

Other cytogenetic abnormalities, such as missing genes, added genes, or genetic rearrangements, may have prognostic significance in CLL (e.g., 11q– deletion, 13q– deletion, +12 multiple copies, 17p– deletion [TP53]) (Byrd, Stilgenbauer, & Flinn, 2004; Wierda, 2006). In addition, identifying the t(11;14) translocation can help to distinguish mantle cell lymphoma from CLL. Patients with 11q– and 17p– tend to have very aggressive disease, whereas patients with 13q– usually have indolent disease. An additional gene on chromosome 12 indicates that patients probably will respond to therapy but will have a brief remission duration. The presence of p53 mutations indicates a probable poor response to alkylating agents and purine analogs (Byrd et al., 2004; Dohner et al., 1995; NCCN, 2006; Wierda).

**Treatment**

**Early stage:** No data have revealed that early treatment of asymptomatic patients with CLL results in survival benefit; therefore, observation is a reasonable approach for patients with no symptoms and "low-risk" disease. A well-documented group of patients have “smoldering CLL,” with extremely slow progression and survival similar to age-matched control populations (Abbott, 2006). Patients with smoldering CLL tend to have Rai stage 0 disease, a lymphocyte count less than 30,000/mcl, normal hemoglobin, and lymphocyte doubling times of more than one year. Such patients should be observed without therapy (Abbott; Rai et al., 2004).

**Later stages:** No globally accepted treatment algorithms or standard approaches exist for patients with CLL, leaving individualized therapy for each patient to the discretion of the oncology healthcare team. Each patient’s risk factors, age, and overall health status will guide treatment choices initially and at each relapse (Abbott, 2006). Many clinicians follow the 1996 National Cancer Institute Working Group guidelines for initiating therapy (Cheson et al., 1996). NCCN (2006) recommended that patients meet one or more of the following indications for treatment; eligible for a clinical trial, has autoimmune cytopenia, has recurrent infections, has B symptoms, has threatened end-organ function, has cytopenias, has bulky disease, is experiencing steady disease progression, prefers treatment, and has experienced histologic transformation. If one or more is present, treatment can include any of the following (NCCN).

- **Clinical trial**
- **Purine analog, with or without rituximab, with or without alkylating agent**
  - Fludarabine single agent
  - Fludarabine with rituximab
  - Fludarabine with cyclophosphamide
  - Fludarabine and cyclophosphamide plus rituximab (Keating et al., 2005)
- **Alkylating agent therapy, single agent**
  - Chlorambucil with or without prednisone
- **Monoclonal antibody with or without cytokine**
  - Rituximab with sargramostim (Ferrajoli et al., 2005)
  - Alemtuzumab
- **Palliative radiation therapy**

**Chemotherapy**

Until purine analogs were introduced in the mid-1980s, alkylating agents were the mainstay of CLL therapy, and chlorambucil was the best-known treatment until the introduction of monoclonal antibodies. Chlorambucil induces partial remissions in about 60% of previously untreated patients but few complete remissions (Wierda, 2006). Alkylator or anthracycline combinations such as CVP (cyclophosphamide, vincristine, and prednisone) and CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) produce similar response rates but offer no survival advantage (Byrd et al., 2004; Dighiero et al., 1998). Alkylating agents cause significant myelosuppression and greater risk of secondary acute myeloid leukemia and are no longer considered the gold standard of CLL therapy, but they continue to play a role in the treatment of CLL as single agents and as part of combination therapy (Abbott, 2006; Wierda).

Purine analogs (e.g., fludarabine, pentostatin [Nipent®, Mayne Pharma, Paramus, NJ], cladribine) have significant activity against CLL, producing higher percentages of complete remissions and longer progression-free survival than chlorambucil (Byrd et al., 2004; Wierda, 2006). Fludarabine is the most widely used and studied of the agents in the United States (for study reviews, see Abbott [2006] and Wierda). Fludarabine is approved by the FDA for the treatment of patients with B-cell CLL who have not responded to or whose disease has progressed after treatment with standard alkylating agent therapy (Berlex, 2003).

Purine analogs have antitumor activity as single agents in patients with previously untreated CLL and refractory CLL. Single-agent fludarabine produces higher response rates and longer remissions than chlorambucil, CHOP, and CVP (Wierda, 2006). For example, Rai et al. (2000) randomized 509 patients to receive fludarabine, chlorambucil, or both. Patients in the combination arm experienced unacceptable toxicity, so it closed early. However, the complete response rate in the fludarabine arm was 20% versus 4% in the chlorambucil arm; overall response rates were 63% versus 37%. Patients who received fludarabine experienced median remission durations of 25 months, nearly twice as long as those in the chlorambucil arm. Nevertheless, overall survival was not significantly different in the two arms (Rai et al., 2000).

In recent studies, purine analogs have shown even higher response rates in combination regimens (Abbott, 2006; Ferrajoli & Keating, 2004). Researchers have tried to exploit fludarabine’s ability to enhance the activity of cyclophosphamide, and in a variety of trials, the combination has produced higher complete response rates and overall response rates than fludarabine alone. In Eichhorst et al.’s (2006) study, the complete response rate was 24% versus 7%, with mean remission durations of 48 versus 20 months. Many clinicians are using fludarabine in first-line therapy and in combinations because of NCCN (2006) recommendations based on positive clinical trial results.

Fludarabine generally is well tolerated, but its side effects can be severe. Myelosuppression may occur, making patients...
susceptible to bacterial and fungal infections. Major lymphosuppression also may occur, requiring prophylaxis for Pneumocystis carinii and herpes simplex. Major side effects include hematologic and immunologic toxicities. Autoimmune hemolytic anemia also has been observed. Long-term hematopoietic stem cell damage may persist, and rare reports of acute myeloid leukemia following treatment exist (Abbott, 2006; Wierda, 2006).

Monoclonal Antibodies

**Rituximab:** Rituximab is a chimeric monoclonal antibody that binds CD20, which is found on the surface of normal and malignant B cells. With the introduction of rituximab and its apparent success in treating other forms of non-Hodgkin lymphoma, clinicians have explored its use in CLL. Rituximab is approved by the FDA for the treatment of patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell, non-Hodgkin lymphoma; first-line treatment of follicular, CD20-positive, B-cell non-Hodgkin lymphoma in combination with CVP chemotherapy; treatment of low-grade, CD20-positive, B-cell non-Hodgkin lymphoma in patients with stable disease or who achieve a partial or complete response following first-line treatment with CVP chemotherapy; and first-line treatment of diffuse large B-cell, CD20-positive, non-Hodgkin lymphoma in combination with CHOP or other anthracycline-based chemotherapy regimens (Genentech BioOncology, 2005). Rituximab is not approved for the treatment of CLL.

CD20 is not strongly expressed in CLL, and rituximab has a reduced target in that condition (Huhn et al., 2001). In a major early trial, rituximab showed poor outcomes in patients with CLL (Huhn et al.). Later studies have indicated that rituximab does have some activity and efficacy in CLL. Although positive response rates have been reported, responses generally have been of short duration (Lin et al., 2004; Lin, Lucas, & Byrd, 2003).

In one clinical trial, rituximab was administered three times a week for four weeks at standard doses (up to 2,250 mg/m²), and in another trial, the drug was administered in very large doses weekly for four doses. The three-times-a-week regimen produced a 45% overall response rate in previously treated patients (Byrd et al., 2001). In a dose-escalation study, groups of patients received increasing doses of rituximab weekly for four doses. Response correlated with dose, and 75% of the patients who received the highest dose responded (O’Brien et al., 2001). Another trial administered rituximab at standard doses on a weekly schedule for four weeks. Patients who responded or had stable disease were treated every six months for a total of four courses. After the first course, the response rate was 51%, with 4% experiencing complete responses (Byrd et al., 2003).

In a trial reported in 2003, rituximab was administered as first-line therapy in CLL. The trial confirmed that although patients may respond to rituximab, most responses are partial. At six weeks, 20 patients (47%) had achieved a partial response, 21 (49%) had stable disease, and only 2 (4%) achieved a complete response. After follow-up, 9% experienced a complete response, 49% had a partial response, and 42% had stable disease. Median progression-free survival was 18.6 months (Hainsworth et al., 2005).

Other current clinical trials are combining rituximab with fludarabine and other chemotherapy to assess their effects in CLL (see Table 2). Rituximab is believed to improve the activity of fludarabine and other purine analogs because it may sensitize leukemia cells to fludarabine-induced apoptosis. Conversely, fludarabine down-modulates the expression of complement-resistance proteins on malignant B cells, making them responsive to rituximab-induced, complement-dependent cytotoxicity (Wierda, 2006). The various combinations, including the purine analog pentostatin, remain under investigation; to date, none has demonstrated clear superiority.

Rituximab infusion-related side effects, including chills, fever, and rigors, are common in patients with CLL. Infusion must be stopped in the case of infusion reactions, although it often can be resumed at 50% of the previous dose once the reaction has been managed. Other adverse events include tumor lysis syndrome, mucocutaneous reactions, allergic reactions, and cytokine-release reaction. Because rituximab depletes B cells, patients may experience reduced serum immunoglobulins and become susceptible to infection. In addition, grade 3–4 cytopenias have developed in about half of patients. Finally, about 40% of patients may experience respiratory system problems such as cough, rhinitis, dyspnea, or sinusitis (Genentech BioOncology, 2005).

**Alemtuzumab:** Alemtuzumab (Campath, Berlex) is a humanized anti-CD52 monoclonal antibody. CD52 is expressed on all lymphocytes (B cells, T cells, and natural killer cells), monocytes, macrophages, and some granulocytes (Lin et al., 2004). The FDA approved alemtuzumab for the treatment of patients with B-cell CLL who have been treated with alkylating agents and failed fludarabine therapy (Berlex, 2005). The recommended alemtuzumab dosage is 30 mg three times per week for 4–12 weeks, with a dose-increase schedule to 3 mg on day 1, 10 mg on day 2, and 30 mg for all doses thereafter (Berlex, 2005).

Alemtuzumab has been studied most often in patients with fludarabine-refractory CLL (Ferrajoli & Keating, 2004). In the pivotal licensing trial with fludarabine-refractory patients, a 35% response rate was reported, with a median time to progression of 9.5 months (Keating et al., 2002).

CAM307, a phase III trial comparing alemtuzumab to chlorambucil as front-line therapy for patients with progressive CLL, has demonstrated marked superiority of alemtuzumab. In the trial, 297 patients were randomized to receive alemtuzumab for up to 12 weeks or oral chlorambucil once every 28 days for a maximum of 12 months. Among the alemtuzumab-treated patients, the complete response rate was 30.9%, but it was only 4.1% for the chlorambucil patients. The 76.5% overall response rate for alemtuzumab was double that seen for chlorambucil (Hillmen et al., 2006).

Lundin et al. (2002) reported an overall response rate of 81%, with a median time to treatment failure of at least 18 months, in previously untreated patients receiving up to 18 weeks of therapy. The trial demonstrated that alemtuzumab could successfully clear disease from blood and bone marrow. It also was significant because the trial showed that subcutaneous administration eliminated infusion-related side effects, although local injection-site reactions still occurred (Lundin et al.). In addition, studies have reported that alemtuzumab is particularly effective in patients with chromosome 17p deletions on fluorescence in-situ hybridization, which are associated with rapidly symptomatic disease and poor survival rates (Lin et al., 2004).
Alemtuzumab is the only FDA-approved agent that reportedly has activity in patients whose leukemia lacks p53 function (Stilgenbauer & Dohner, 2002; Stilgenbauer et al., 2005). The 17p deletion causes p53 inactivity, and patients with the deletion are resistant to chlorambucil, purine analogs, and rituximab.

Like rituximab, researchers are studying alemtuzumab in combination regimens. Small trials have examined the potential efficacy of FluCam (fludarabine followed by alemtuzumab), for example. In one group of 36 previously treated patients, the complete response rate was 30% and the partial response rate was 53%, with a median time to progression of 13 months and overall survival of 35 months (Elter et al., 2005). In another trial, patients received alemtuzumab followed by fludarabine, and the complete response rate was 11%, with an overall response rate of 44%. A different combination, CFAR (cyclophosphamide, fludarabine, alemtuzumab, and rituximab), also is in testing in which patients receive all four agents concurrently. To date, a 27% complete response rate and a 65% overall response rate have been documented (Wierda, O’Brien, Ferrajoli, et al., 2005).

Infection is the major complication of alemtuzumab in all settings, prompting prophylaxis recommendations against Pneumocystis pneumoniae and varicella zoster with oral agents such as trimethoprim/sulfamethoxazole and valacyclovir (Valtrex®, GlaxoSmithKline, Research Triangle Park, NC). In addition, patients should be monitored for cytomegalovirus reactivation during administration and for a minimum of two months after alemtuzumab therapy. Although CD52 is not expressed on platelets, red cells, neutrophils, or their precursors, alemtuzumab has profound hematologic toxicity. Alemtuzumab clears B cells and T cells. Thirty-five percent of patients experience thrombocytopenia, 26% neutropenia, and 21% anemia. Patients with significant cytopenias have a higher incidence of severe infectious complications (Abbott, 2006; Berlex, 2005; Rai et al., 2004). Infusion-related side effects occur in more than 90% of patients receiving alemtuzumab. Most infusion events are mild and more prevalent during the first infusion. Subcutaneous alemtuzumab has a much lower incidence of side effects, although that route of administration is not currently approved by the FDA (Berlex, 2005).

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**Table 2. Rituximab Combination Clinical Trials: Chronic Lymphocytic Leukemia**

<table>
<thead>
<tr>
<th>STUDY</th>
<th>TREATMENT</th>
<th>PRIOR TREATMENT</th>
<th>COMPLETE RESPONSE (%)</th>
<th>OVERALL RESPONSE (%)</th>
</tr>
</thead>
</table>
| Keating et al., 2005; Wierda, O’Brien, Wen, et al., 2005 | Fludarabine, cyclophosphamide, and rituximab | 50% yes  
50% no | 70 (NPT)  
25 (YPT) | 95 (NPT)  
73 (YPT) |
| Byrd et al., 2003 | Concurrent fludarabine plus rituximab followed by rituximab | No | 47 | 90 |
|                    | Sequential fludarabine and two-month rest followed by rituximab | No | 28 | 77 |
| Kay et al., 2004   | Pentostatin, cyclophosphamide, and rituximab   | No | 33 | 97 |
| Lamanna et al., 2006 | Pentostatin, cyclophosphamide, and rituximab  | No | 25 | 75 |

NPT—no previous therapy; YPT—yes, previous therapy

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**Hematopoietic Stem Cell Transplantation**

Despite important progress in the management of B-cell CLL, the only curative option remains allogeneic hematopoietic stem cell transplantation (HSCT) (Abbott, 2006). The goal of allogeneic HSCT is to prolong survival and offer cure to some patients. Improvements in transplantation procedures have permitted the increase of upper age limits for various types of transplants, making transplantation a potential option for as many as two-thirds of patients with CLL at some point in their disease course. In addition, identifying patients with high-risk CLL is becoming easier because of the development of immunoglobulin Vn mutational status testing and the availability of other prognostic indicators (Montserrat, 2004). The major concern in autologous transplantation is the contamination of reinfused stem cells with CLL cells. Varieties of in vivo and ex vivo purging strategies are being explored to minimize the problem. In general, patients treated into good remissions with little to no detectable disease at the time of entry into transplant have better outcomes. However, relapse is common in all groups, with 50% of patients relapsing within four years and 80% after eight years (Montserrat). Allogeneic stem cell transplantation generally shows a plateau in overall and disease-free survival in 40%–60% of patients at four to five years after transplantation, including fully myeloablative standard approaches and nonmyeloablative versions (Montserrat).

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**Clinical Trial Update**

Many novel agents are under investigation for the treatment of CLL. For example, GX15-070 (GeminX, Malvern, PA) is a synthetic small molecule that inhibits the binding of the antiapoptotic proteins bcl-2, bcl-xL, bcl-w, and mcl-1 to the proapoptotic proteins bax and bak, activating programmed cell death in transformed cells (O’Brien et al., 2005). A small phase I trial demonstrated that the agent has dose-dependent activity in CLL, and further trials are planned (O’Brien et al., 2005). Laboratory studies have shown that humanized anti-CD40 antibody SGN-40 (Seattle Genetics, Bothell, WA) induces cytotoxicity against CLL cells through antibody-mediated cytotoxicity (ADCC) (Gowda et al., 2005). In addition, the fully human anti-CD40 monoclonal
Flavopiridol (Sanofi-Aventis, Bridgewater, NJ), a synthetic flavone, inhibits cyclin-dependent kinases 1, 2, 4, and 9 and thereby inhibits proliferation and stimulates apoptosis. A recently reported phase I trial demonstrated activity in heavily pretreated patients who had bulky disease and poor-risk cytogenetics. Fifty percent of the patients experienced at least a partial response, with a median duration of progression-free survival of 11 months. The trial was testing a dosing schedule designed to overcome drug binding to plasma proteins (Lin et al., 2006).

Lenalidomide (Revlimid®, Celgene Corporation, Summit, NJ), a thalidomide analog, recently was approved for the treatment of myelodysplastic syndrome and multiple myeloma. It is under intensive study in many other indications, including CLL. Ferrajoli et al. (2006) reported a clinical trial in which lenalidomide induced one complete and seven partial responses in second-line therapy for 35 patients with CLL. The major toxicity was myelosuppression (Ferrajoli et al., 2006). Another trial of single-agent lenalidomide also demonstrated clinical activity, with partial and complete responses. One distinctive feature of the trial, however, was that the addition of rituximab to the regimen restored responsiveness in patients who developed resistance to lenalidomide (Chan-Chan, 2006).

Combination therapy regimens are a very important focus of investigation, but reviewing all of the current clinical trials would be virtually impossible. The central agents usually are fludarabine and either rituximab or alemtuzumab, and most studies report encouraging findings. One of the most common combinations is fludarabine with alemtuzumab. See Table 3 for a sample of the results reported in 2006.

### Nursing Implications

Both the disease process of CLL and its treatment can lead to serious and challenging complications for oncology nurses, who must understand the natural history, prognostic indicators, and treatment approaches for CLL to be prepared to anticipate problems and care for and guide patients through the disease continuum. Because of the high risk of infection in patients with CLL, nurses must provide intensive and ongoing education to patients and caregivers about simple infection-control measures,

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**Table 3. Combination Regimens for Chronic Lymphocytic Leukemia: Selected Trial Reports**

<table>
<thead>
<tr>
<th>STUDY†</th>
<th>REGIMEN</th>
<th>DISTINCTIVE FINDINGS</th>
</tr>
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<tbody>
<tr>
<td>Delmer et al., 2006</td>
<td>Subcutaneous alemtuzumab after oral fludarabine and cyclophosphamide (FC)</td>
<td>Alemtuzumab was used to consolidate responses after FC. Three courses of FC gave a high response rate in older adult patients, and alemtuzumab afterward greatly reduced minimal residual disease.</td>
</tr>
<tr>
<td>Faderl, Ferrajoli, et al., 2006</td>
<td>Alemtuzumab (IV followed by subcutaneous injection) and rituximab</td>
<td>Thirty-two patients were evaluable, and all relapsed. The overall response rate was 50%, with 25% complete responses. The regimen generally was well tolerated, although 56% had infusion reactions and 22% had reactivation of cytomegalovirus. Responses occurred after only four weeks.</td>
</tr>
<tr>
<td>Faderl, Wierda, et al., 2006</td>
<td>Fludarabine, cyclophosphamide, mitoxantrone (Novantrone®, Immunex, Seattle, WA), and rituximab</td>
<td>Thirty-one patients were enrolled; a 97% response rate was noted at three months, with 41% complete responses. Neutropenia required the use of hematopoietic growth factors throughout therapy.</td>
</tr>
<tr>
<td>Mauro et al., 2006</td>
<td>Fludarabine, cytarabine, mitoxantrone, and dexamethasone with alemtuzumab</td>
<td>Nineteen patients were enrolled. Partial or complete responses were noted in almost all patients. Infection was almost universal as a complication of treatment.</td>
</tr>
<tr>
<td>Mena et al., 2006</td>
<td>Pentostatin, cyclophosphamide, and rituximab (PCR)</td>
<td>Fifty patients were evaluable. The overall response rate was 52%, and the complete response rate was 8%. Low toxicities were reported.</td>
</tr>
<tr>
<td>Sayala et al., 2006</td>
<td>Alemtuzumab with fludarabine</td>
<td>Fifty-three patients were enrolled. Subcutaneous alemtuzumab was effective in refractory chronic lymphocytic leukemia and well tolerated. The median survival for responders was 25 months. The addition of fludarabine, given to nonresponders and partial responders, improved response rates with acceptable toxicity.</td>
</tr>
<tr>
<td>Shanafelt et al., 2006</td>
<td>PCR</td>
<td>Sixty-four patients were enrolled. PCR was well tolerated by patients older than age 70, with good performance status, and with creatinine clearance &lt; 70. The overall response rate was 83%–93%, and the complete response rate was 40%.</td>
</tr>
<tr>
<td>Wierda et al., 2006</td>
<td>Cyclophosphamide, fludarabine, alemtuzumab, and rituximab</td>
<td>Seventy-nine patients were enrolled, and 74 completed treatment. All patients were pretreated heavily. The overall response rate was 65%, with 24% complete responses. In all patients with complete response, minimal residual disease was undetectable. The median survival time was 19 months, and the time to progression was 32 months for complete responses and 18 months for partial responses.</td>
</tr>
</tbody>
</table>

*All studies were phase II except Mauro et al. (2006), which was phase I.*
such as good hand washing, pneumonia vaccines, and yearly flu immunizations for patients and caregivers. Patients and caregivers also must be well versed on reportable signs and symptoms of infection based on their current treatment plans, disease states, and overall medical and immune system status. Patients with CLL may not present with typical signs and symptoms of infection because of impairments in immune system functioning and triggering mechanisms.

The bleeding prejudices, lifestyle changes, and medication assessments outlined in nursing implications for ITP all apply to patients with CLL during periods of disease- or therapy-induced thrombocytopenia. Similarly, patients should be encouraged to wear alert bracelets to ensure that their history is known during any emergencies.

Ongoing chemotherapy and biotherapy teaching is a critical part of oncology nurses’ role in caring for patients with CLL. Each drug carries a unique side-effect profile, which is important information for patients and caregivers, regardless of how heavily pretreated patients may be. In particular, the most commonly used agent, alemtuzumab, carries a high risk of infection, and patients should receive prophylaxis against bacterial and viral agents. In addition, patients with CLL should have clear understandings of objective and subjective triggers for red cell and platelet transfusions. They should be prepared to anticipate requiring transfusions at some point in their disease process. Any personal beliefs opposing or limiting transfusion or growth factor support should be identified early in the disease process. Therapies may be avoided or doses modified to lessen the projected need for such interventions.

Oncology nurses need to possess a thorough understanding of the mechanisms of action of targeted therapies to effectively care for patients receiving these agents, as well as to educate patients and caregivers. Clearly, a great deal of research is focusing on targeted approaches, both as single agents and in combination with standard chemotherapy. The frequent introduction of new regimens, as well as the increasing number of clinical trials, will continue to pose a challenge for oncology nurses in maintaining their information. Nurses also must be aware of new measurement and testing for diagnosis, prognosis, and response, such as minimal residual disease.

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