FEATURE ARTICLE

Introduction to B-Cell Disorders

Kimberly Noonan, RN, AOCN®

Healthcare professionals have a good understanding of B cells in normal immunity. Although the role of lymphocytes and the lymphoid system in lymphoma is understood, the role of B cells is less clear in several autoimmune diseases, such as rheumatoid arthritis, idiopathic thrombocytopenic purpura, and autoimmune hemolytic anemia. This article will present an overview of malignant and nonmalignant B-cell disorders. Experts hypothesize that some monoclonal antibodies can deplete the B-cell population and prevent B- and T-cell responses in autoimmune diseases. Nurses should understand the data surrounding monoclonal therapy, which are not always presented clearly. Nurses’ ability to interpret data is important to their patients and colleagues.

The understanding of B cells in normal immunity has grown. Unlike the role of lymphocytes and the lymphoid system in lymphoma, the role of B cells is less clear in several autoimmune diseases, such as rheumatoid arthritis (RA), idiopathic thrombocytopenic purpura (ITP), and autoimmune hemolytic anemia (AIHA). This article will present an overview of malignant and nonmalignant B-cell disorders. In the second article in this supplement, “Treatment Approaches and Nursing Applications for Non-Hodgkin Lymphoma (NHL),” Jennifer M. Long, APRN, will focus on treatment options for NHL. The third article, written by Amy Goodrich, CRNP, will present “Emerging Therapeutic Options for B-Cell Disorders,” discussing ITP and chronic lymphocytic leukemia (CLL). The articles will provide a foundation for the final article, “Cytokine-Release Syndrome,” written by Sheila Breslin, RN, MS.

B-Cell Development

Lymphocytes are the main cells involved in the immune system. The two types of lymphocytes are B cells and T cells. T lymphocytes are needed for cell-mediated immunity. T lymphocytes activate other T and B cells and often are associated with delayed hypersensitivity and graft rejection. B lymphocytes are responsible for humoral immunity. Humoral immunity is an essential function of immunity; it eliminates bacteria, prevents viral infections, neutralizes bacterial toxins, and plays an important role in certain allergic reactions (Sommers, 2005). An important role of B lymphocytes in the immune system is to produce antibodies. Figure 1 demonstrates the development of a B cell. B lymphocytes begin as stem cells found in the bone marrow. The stem cells develop into immature pro B cells, followed by pre B cells, immature B cells, and finally mature B cells.

Lymphocytes recognize and respond to foreign antigens. A subset of cell surface molecules or antigens is found on the surfaces of leukocytes and can be recognized by a specific set of antibodies.

At a Glance

✦ Understanding of the pathophysiology of immunity and the importance of T and B cells in autoimmune diseases has grown.

✦ Nurses should be familiar with nonmalignant B-cell disorders and standard treatment options as well as new approaches for patients with nonmalignant B-cell disorders.

✦ Malignant B-cell disorders include chronic lymphocytic leukemia, Waldenstrom macroglobulinemia, and non-Hodgkin lymphoma, and this article discusses treatment options for each disease.

The role of B lymphocytes in B-cell disorders is complex. B cells are essential to regulate the immune system. They are antibody producing and are responsible for autoantibodies that are directly or indirectly destructive (Robak, 2004). B cells

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act as antigen-presenting cells (APCs), and they allow optimal development of memory in the T-cell population. In addition, B cells may provide support to other mononuclear cells, as well as contribute to the inflammatory process (Carter, 2006; Sommers, 2005). B cells may produce inflammatory procytokines such as tumor necrosis factor-α, interleukin-6, and immunoregulatory cytokines such as interleukin-10 (Dorner, 2006).

B cells’ importance in adaptive immunity can be understood further by a review of the pathophysiology of immunity. The major histocompatibility complex (MHC) molecules recognize self from nonself. MHC is comprised of class I and II MHC molecules. APCs are part of MHC II. APCs aid the immune system in processing antigens. MHC II molecules are found primarily on APCs such as macrophages, dendritic cells, and B lymphocytes. APCs communicate with antigen receptors and molecules on helper T lymphocytes. Figure 2 describes the immune pathway.

**Targeted Therapy in B-Cell Disorders**

Rituximab (Rituxan®, Genentech BioOncology, South San Francisco, CA) is a monoclonal antibody (MOAB) designed to destroy the CD20 antigen, which is found on B lymphocytes. The U.S. Food and Drug Administration (FDA) approved rituximab in 1997. The drug initially was used exclusively in patients with follicular lymphoma, but since its approval, rituximab has proven effective in all B-cell lymphomas that are CD20+. The MOAB response mechanism cells are destroyed in three ways: complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and apoptosis (programmed cellular death). Complement-dependent cytotoxicity causes enzymatic reactions that play an important role in mediating inflammation, phagocytosis, and cytolysis. Antibody-dependent cell-mediated cytotoxicity mobilizes the body’s effector cells such as macrophages, monocytes, and natural killer cells that seek and destroy targeted cells. Figure 3 describes that mechanism of action.

Rituximab has been used successfully in patients with autoimmune diseases such as ITP, AIHA, and RA. Some experts hypothesize that MOABs, such as rituximab, can deplete the B-cell population and prevent B- and T-cell responses in autoimmune diseases (Isenberg, 2006).

**Nonmalignant B-Cell Disorders**

**Idiopathic Thrombocytopenic Purpura**

ITP is an immune-mediated disorder in which platelets are damaged by autoreactive antibodies and destroyed prematurely by the reticuloendothelial system (Stasi & Provan, 2004). ITP often is defined as a platelet count less than 50,000/mm³. In children, ITP may present as an acute disease often associated with viral infections or immunizations. In young populations, males and females are affected equally and ITP resolves in approximately 70% of cases. In contrast, ITP in adults has an insidious onset, often is a chronic disorder, and usually is not associated with viral infections.

Adult ITP is more common in women (occurring two to three times more often) and occurs most often from ages 18–40 years. Symptoms range from mild bruising to abrupt hemorrhage. Diagnosis commonly is an incidental finding discovered during routine examination. ITP can be confused with other thrombocytopenic disorders, including thrombotic thrombocytopenia purpura and lymphoproliferative disorders. Medications such as heparin and quinidine are just a few of many that can cause thrombocytopenia. Bleeding disorders and infections such as HIV or hepatitis C also can cause a decrease in platelets.

Many clinicians treat ITP when platelet counts range from less than 20,000–30,000/mm³. Patients initially are treated with
oral prednisone. Prednisone affects ITP by inhibiting antibody production, increasing platelet production, and impairing the clearance of antibody-coated platelets by tissue macrophages (Stasi & Provan, 2004). The incidence of continuous remission is reported to be 5%–30%. In prednisone-refractory patients, IV immunoglobulin therapy can be used. In such clinical situations, splenectomy should be considered. Splenectomy can provide complete remission in approximately 66% of patients (Shanafelt, Madue, Wolf, & Tefferi, 2003; Vesely, Perdue, Rizvi, Terrell, & George, 2004).

Many medications can be used to control ITP. Rituximab therapy can deplete B cells that may involve autoreactive B cells. Response rates have been reported in more than 50% of patients, with 25% sustained responses (Stasi, Pagano, Stipa, & Amadori, 2001). Other medications also have proven activity in ITP, including danazol, azathioprine, cyclophosphamide, vinca alkaloids, and cyclosporin.

Autoimmune Hemolytic Anemia

AIHA is characterized by the presence of pathologic antibodies against an individual's own red blood cell antigens or autoantibodies. AIHA causes an accelerated destruction of red blood cells (Alvardi & Klein, 2005; Robak, 2004). Warm agglutinin AIHA is approximately four times as common as hemolysis from cold agglutinin AIHA. Cold agglutinins can be caused by infection such as mycoplasma and infectious mononucleosis or in response to a paraneoplastic process. Warm agglutinin AIHA often is associated with a collagen vascular disease such as lupus erythematosus or lymphoproliferative disease such as CLL.

Patients often present with hematocrit of 21%–30% and hemoglobin of 7–10 g/dl. The most important laboratory test to determine AIHA is the direct antiglobulin or Coombs' test. The test will detect antibodies or complements that are coating the red blood cells and, if positive, may suggest immune destruction. Bone marrow smears may show an increase in the ratio of erythrocytes to granulocytes. Other laboratory tests that suggest hemolysis are an increase in reticulocytes and lactic dehydrogenase (LDH) and a decrease in haptoglobin.

The treatment of AIHA is similar to that for ITP. Nonpharmacologic treatment includes avoidance of the cold (cold agglutinin disease), infusion of red blood cells, plasmapheresis, and splenectomy. Pharmacologic interventions include corticosteroids and IV immunoglobulins, which are given with proven benefit (Alvardi & Klein, 2005). Alkylating agents such as cyclophosphamide, purine analogs, and interferon have been used with marginal results. Rituximab has been used with promising results in patients with AIHA caused by lymphoproliferative disorder (Berentsen et al., 2004).

Rheumatoid Arthritis

RA is an autoimmune disease described as a chronic systemic inflammatory disorder of unknown etiology that primarily involves joints. RA is a complex disease with enhanced activation of immune cells, including B cells (Dorner, 2006). RA is symmetrical and uncontrolled, which often leads to destruction of joints because of erosion of cartilage and bone, ultimately causing bone deformity. RA affects women two to three times more often than men. The peak onset of RA occurs in patients aged 30–55 years. RA may have periods of remission followed by exacerbations. Patients usually present with morning stiffness (lasting for at least one hour), symmetrical swelling of three or more joints, and swelling of the wrist, metacarpophalangeal, or proximal interphalangeal joints for six weeks or more. Hand x-rays show changes typical of RA, including erosions, unequivocal bony decalcifications, and subcutaneous nodules. About one-third of patients present with generalized myalgia, fatigue, low-grade fever, weight loss, and depression (Lee & Weinblatt, 2001).

No single test is used to diagnose RA. Diagnosis often is made with a combination of laboratory, radiologic, and clinical data. Rheumatoid factors are found in 70%–80% of patients with RA. Anticyclic citrullinated peptide antibodies, erythrocyte sedimentation rate, and C-reactive proteins often are elevated in patients with RA. Cartilage and bone erosion are important findings when diagnosing RA. Erosions can be found on plain films, but magnetic resonance imaging may be needed.

The disease trajectory is known to fluctuate over periods of time lasting from weeks to months. Patients treated with disease-modifying antirheumatic drugs within a year of disease onset are likely to achieve remission within three to five years.
(Gossec et al., 2004). Treatment of RA includes the use of drugs and nonpharmacologic interventions such as rest, exercise, physical therapy, and occupational therapy. RA is associated with complications related to sedentary lifestyle; therefore, nutrition and dietary interventions should be considered. Bone integrity can be compromised by prolonged steroid use and also should be evaluated.

Pharmacologic interventions include five main classes of drugs: analgesics, nonsteroidal anti-inflammatory drugs, glucocorticosteroids, disease-modifying antirheumatic drugs, and anticytokines. The specific medications are listed in Figure 4. In February 2006, rituximab was approved by the FDA for use in patients with RA. A phase II trial compared rituximab alone to rituximab plus methotrexate, rituximab plus cyclophosphamide, and methotrexate alone. Rituximab was given at a dose of 1,000 mg/m² as a one-time infusion on days 1 and 15. All groups received corticosteroids. The rituximab comparative groups had higher symptom response rates of 65%, 76%, and 73%, respectively; the group receiving methotrexate alone had a symptom response rate of 38% (Edwards et al., 2004).

**Malignant B-Cell Disorders**

**Chronic Lymphocytic Leukemia**

CLL is a neoplasm of small, round B lymphocytes accompanied by larger cells known as prolymphocytes and expressing B-cell antigens that are positive for CD5 and CD23. Once believed to be a different disease, small lymphocytic lymphoma now is believed to be the same disease manifested in different ways (Gribben, Harris, & Dalla-Favera, 2005). CLL is considered to be a disease of the aging. Approximately 7,000 people are diagnosed in the United States every year. The median age at diagnosis is 70 years. One of the strongest risk factors for CLL appears to be a family history of CLL or any B-cell malignancy.

The diagnosis of B-cell CLL often is an incidental finding during routine primary care, when a painless, enlarged lymph node is discovered or a complete blood cell count shows lymphocytosis greater than 5,000/mcl. Flow cytometry can be obtained on peripheral blood or bone marrow to detect a clonal population of small round lymphocytes, which supports the diagnosis of CLL (Wierda & O’Brien, 2006). Other clinical findings include splenomegaly, hepatomegaly, anemia, and mild thrombocytopenia. An estimated 25% of all patients feel well at diagnosis. However, approximately 5%-10% report B symptoms (night sweats, fevers without infection, and weight loss more than 10% of body weight in the past six months). Patients also may report extreme fatigue and a significant decrease in performance status (Wierda & O’Brien).

The single most important prognostic indicator is stage of disease at diagnosis. Rai (stages 0-IV) and Binet (stages A, B, and C) are two staging systems that often are used to stage patients with CLL. The median survival time for stage Rai 0 or Binet A (low-risk disease) is 10-12 years, compared to 1-3 years for stage Rai IV or Binet C (high-risk disease) (Seiler, Dohner, & Stilgenbauer, 2006).

Currently, standard therapy for CLL is not curative, although considerable treatment advances have been made since 2000 (Lin, Grever, & Byrd, 2005). Treatment often is deferred until disease progression warrants intervention. To date, research does not support survival advantages of early treatment when compared to monitoring without treatment. Therapy often is contingent on therapeutic goals and quality of life. The span of treatment ranges from chemotherapy consisting of purine analogs, alkylating agents, and MOABs to stem cell transplantation. The addition of rituximab to chemotherapy is associated with better outcomes. A Cancer and Leukemia Group B protocol comparing fludarabine to fludarabine plus rituximab reported superior progression-free survival and overall survival in the fludarabine plus rituximab group (Byrd et al., 2005). In aggressive or refractory CLL, allogeneic stem cell transplantation may be associated with long-term survival. However, mortality rates often are unacceptable.

**Waldenstrom Macroglobulinemia**

Waldenstrom macroglobulinemia (WM) is a clinical syndrome associated with B lymphocytes and plasma cells (often identified by lymph node or bone marrow biopsies). This is reported as lymphoplasmacytic in appearance. Other findings may be the presence of elevated monoclonal immunoglobulin and symptoms of hyperviscosity. The syndrome often is confused with lymphoplasmacytic lymphoma; distinguishing between the two disorders can be difficult. WM is a rare disease that is diagnosed most often in older adults (Dimopoulos, Panayiotidis, Moulopoulos, Sfikakis, & Dalakas, 2000).

The etiology of WM is unknown, but an association exists between the disorder and occupational exposure to paints, leather, and rubber dyes. Common symptoms of WM are fatigue related to anemia, bleeding, and peripheral neuropathy. Neurologic conditions such as blurred vision, confusion, stroke, and coma may be indicative of hyperviscosity syndrome. Lymphadenopathy and hepatosplenomegaly are clinical findings that are consistent with WM (Rohtainer, Harris, Dalla-Favera, & Lister, 2005).

Obtaining initial blood counts and blood chemistries is important to evaluate renal and liver function. Blood work should include a complete blood count with differential, chemistries, protein electrophoresis, immunoglobulin, beta-2 microglobulins, serum viscosity, cold agglutinins, and cryoglobulins. Bone marrow biopsy may be helpful in detecting infiltrates of small
lymphocytes with a variable degree of plasmacytoid features. Chromosomal translocations of t(9;14)(p13q32) are identified with WM. Computed tomography scans are useful in detecting lymphadenopathy or hepatosplenomegaly (Rohatiner et al., 2005).

WM is a rare disease that occurs in older adults, which makes obtaining data to define prognostic factors difficult. Prognostic factors have been identified as an increase in age, low albumin, and a number of cytopenias. The median survival is five years, although approximately 20% of patients may survive longer than 10 years (Morel et al., 2000).

WM is treated as significant disease progression becomes apparent. Signs and symptoms of disease progression include B symptoms, hyperviscosity, neuropathy, renal impairment, and symptomatic cryoglobulinemia. An increase in immunoglobulin, anemia, and thrombocytopenia are clinical findings that suggest the need for treatment. Significant lymphadenopathy or hepatosplenomegaly also may suggest that treatment is warranted. Quality of life is a consideration when treating WM, as most patients are older and may have comorbidities that limit treatment options.

Hyperviscosity is treated with plasmapheresis as a quick and effective way to reduce immunoglobulin levels. However, plasmapheresis should not be given with chemotherapy or immunotherapy. Purine analogs such as fludarabine and 2-chlorodeoxyadenosine often are used with success but are not curative. Combination chemotherapy such as CHOP (cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisone) has been used without significant improvement in overall survival (Dimopoulos et al., 2000). Thalidomide also has shown activity in the disease, although only low doses were tolerated by the majority of patients studied (Dimopoulos et al., 2001).

Rituximab has clinical activity in WM. Responses were reported in as many as 40% of patients when rituximab was given at a dose of 375 mg/m² for four weeks (Byrd et al., 1999; Dimopoulos et al., 2002; Foran et al., 2000).

**Non-Hodgkin Lymphoma**

About 56,000 new cases of NHL are diagnosed every year. NHL is a neoplastic transformation of normal lymphoid cells, which reside predominantly in lymphoid tissues. NHLs are categorized as T- and B-cell lymphomas. Most B-cell lymphomas have an immunophenotype that is CD20+.

The risk factors associated with B-cell lymphoma include family history, autoimmune diseases such as RA, and organ transplantation requiring immunosuppressive medication. Radiation increased the risk of lymphoma development. Viruses such as human T-cell lymphotropic virus type I, HIV, and Epstein-Barr virus play a significant role in the etiology of lymphoma. The development of *Helicobacter pylori* increases the risk of gastric B-cell lymphoma, known as mucosa-associated lymphoid tissue (Rogers, 2006).

Although most patients present with enlarged lymph nodes, many have B symptoms such as weight loss, night sweats, pruritus, and fevers. Diagnosis is made by the removal of a lymph node, which is sent to a pathology laboratory for investigation by a hematopathologist. History, physical examination, blood work, and scans are needed to accurately stage NHL. The Ann Arbor classification system is used to stage NHL, but more defined classification systems are used for specific types of NHL, such as the International Prognostic Index score for diffuse large B-cell lymphoma (DLBCL) and the Follicular Lymphoma International Prognostic Index score for follicular lymphoma (Rogers, 2006).

Many types of NHL exist, and precise diagnosis is essential to implement appropriate treatment plans. Diagnosis of NHL often is confusing because classification has changed several times. Currently, the World Health Organization Revised European-American Lymphoma classification often is used. The classification considers four important criteria: cellular morphology, immunophenotype, genetic features, and clinical features. NHL is classified as indolent or aggressive, based on natural history of growth (Cheson, 2004).

Indolent lymphoma commonly presents at an advanced stage and transforms into aggressive lymphoma 30% of the time (Rogers, 2006). Immediate treatment of indolent lymphoma offers no survival benefit, and the disease is not cured with standard chemotherapy (Advani, Rosenberg, & Horning, 2004). Treatment options for advanced indolent lymphoma include watchful waiting, external beam radiation therapy, chemotherapy, high-dose or nonmyeloablative chemotherapy with stem cell support, MOAB therapy, and radioimmunotherapy. Investigational treatments such as vaccines are being studied in clinical trials (Hohenstein, King, Fiore, O’Brien, & Blumel, 2005).

The FDA initially approved rituximab for relapsed follicular lymphoma or transformed lymphoma. In a pivotal trial of 166 patients, almost 50% of all patients responded to four weekly doses of rituximab at a dose of 375 mg/m². The duration of response was approximately 11 months (McLaughlin et al., 1998). Since that finding, the use of rituximab for all CD20+ lymphomas and antibody-mediated autoimmune diseases has been studied widely. Rituximab currently is used alone as well as with combination chemotherapy to improve overall response rates (Czuczman, Weaver, Alkuzweny, Berlefein, & Grillo-Lopez, 2004; Marcus et al., 2005).

Aggressive lymphomas can be cured with standard chemotherapy if treated immediately. Approximately 30% of all B-cell lymphomas are DLBCL. The treatment of DLBCL is determined by stage, early or advanced. Patients with early-stage DLBCL often are treated with a combination of chemotherapy such as R-CHOP (rituximab plus CHOP) or CHOP for three cycles plus involved field radiation (Miller et al., 2004). In advanced DLBCL, six to eight cycles of CHOP or R-CHOP are recommended. CHOP has been compared to several other combination treatment regimens, and research supports the efficacy and safety of CHOP over other combination chemotherapies (Bartlett et al., 2001; Fisher et al., 1995). More recently, CHOP has been compared to CHOP plus etoposide, randomized to every 14 or 21 days. CHOP-14 may be an acceptable regimen with a similar toxicity profile when compared to CHOP-21 (Pfreundschuh et al., 2004).

The role of upfront high-dose therapy with autologous stem cell transplantation (ASCT) is controversial in aggressive advanced-stage NHL. Several studies have suggested no benefit from upfront high-dose therapy (Gisselbrecht et al., 2002; Olivieri et al., 2005). A study reported by Milpied et al. (2004) suggested that initial treatment with high-dose therapy after CHOP is superior to CHOP alone. Treatments for high-risk
patients with DLBCL are under investigation. A phase III trial conducted by Groupe d’Etude des Lymphomes D’Adulte is under way to determine the role and most appropriate time for ASCT for patients with DLBCL (Steingass, 2006).

High-dose chemotherapy followed by ASCT support falls into two distinct categories for relapsed aggressive lymphoma: patients who have chemotherapy-responsive disease and patients who do not. The responsive group will have a 50%–50% probability of disease-free survival at three to five years, in comparison to patients with resistant disease, who will have disease-free survival of 10%–20% in three to five years (Hamlin et al., 2003; Vose et al., 2001).

High-dose therapy with stem cell support is controversial in low-grade lymphoma. The natural survival of patients with indolent lymphoma is very long, often extending into decades. An extensive side-effect profile may be difficult to accept by patients who feel well and have the option of ASCT. Some data support ASCT as superior to standard chemotherapy. In a study by Lenz et al. (2004), five-year progression-free survival was 65% in an ASCT group versus 33% in a CHOP plus interferon group. In terms of long-term survival, 69% of 153 patients were alive, after a median of 12 years, following upfront ASCT for follicular lymphoma (Freedman et al., 1999). Stem cell transplantation after transformation of indolent lymphoma to aggressive lymphoma, with responsive disease, is associated with better overall survival of 46%–69% at five years (Friedberg et al., 1999; Williams et al., 2001).

Hodgkin Disease

Hodgkin disease (HD) is a group of lymphoid malignancies commonly characterized by a finding of Reed-Sternberg cells. The diagnosis of HD peaks at two separate stages of life. The first is from the ages 20–30, and the second is after the age of 55. Effective therapy has been developed, and HD is curable about 80% of the time (Ansell & Armitage, 2006). The etiology of HD is unknown, but several risk factors are associated with its development. Although a gene has not been identified, same-gender siblings of patients with HD have a 10-fold chance of developing HD (Ansell & Armitage). Infections such as Epstein-Barr virus and HIV also have been associated with development of HD.

More than 75% of patients with HD present with cervical or supraclavicular lymphadenopathy. Also common is detection of a mediastinal mass on chest x-ray after vague complaints of shortness of breath, cough, or pleuritic chest pain. Other clinical manifestations include splenomegaly and B symptoms such as weight loss, night sweats, and unexplained fevers. Pruritis is not considered a B symptom; however, 10%–15% of patients with HD complain of pruritis. Severe pruritis is considered a poor prognostic indicator (Ansell & Armitage, 2006, Brigle, 2006).

HD is classified by the Revised European-American Lymphoma system. Two distinct types exist. The more common is classic HD, which has a distinct positive immunophenotype of CD15 and CD30, and nodular lymphocyte-predominant HD. Nodular lymphocyte-predominant HD is very rare. The cells have a distinctive difference in the immunophenotype (CD20+) and commonly are negative for CD15 and CD30. Classic HD has four subtypes. Nodular sclerosis is the most common type and occurs in 60%–80% of all cases. The other types of classic HD are mixed cellularity, lymphocyte depletion, and lymphocyte rich.

Staging is very important in HD and determines treatment and prognosis. The Ann Arbor classification system is used to stage the disease. Computed tomography scans of the chest, abdomen, and pelvis and whole-body positron emission tomography can evaluate the extent of the disease. Bone marrow biopsy also can determine the extent of disease present. Laboratory studies such as complete blood cell count, LDH, erythrocyte sedimentation rate, renal and liver function tests, and serum albumin should be obtained initially and monitored throughout treatment. Prognosis is dependent on stage and organ involvement, although other considerations have been described by the European Organization for Research and Treatment. They include large mediastinal mass, elevated erythrocyte sedimentation rate, involvement of three or more lymph node sites, involvement of extranodal sites, and massive splenic disease. Additional prognostic indicators include the presence of bulky disease, increased LDH, severe bone marrow involvement, and poor response to initial treatment (Ansell & Armitage, 2006).

Table 1 describes prognosis related to disease stage.

Radiation can be used alone to treat HD in certain clinical situations. However, the mainstay of treatment includes combination chemotherapy of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) with or without radiation. Other chemotherapy regimens that are used include MOPP (mechlorethamine, vincristine, procarbazine, and prednisone), Stanford V (mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, prednisone, and possibly granulocyte-colony-stimulating factor), and BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone).

The most important concept of HD treatment is to maintain the chemotherapy regimen despite complications such as myelosuppression. Growth-factor support should be given to avoid chemotherapy delays or reductions. Patients who are unresponsive to standard chemotherapy or who relapse after chemotherapy and radiation should be considered for ASCT after receiving salvage therapy (Ansell & Armitage, 2006). Treatment for nodular lymphocyte-predominant HD is very different from treatment for classic HD. In stage IA disease, a lymph node excision followed by radiation or a watch-and-wait approach commonly is used. MOAB therapy has been used successfully in patients with lymphocyte-predominant HD (Rehwald et al., 2003).

### Table 1. Prognosis Based on Stage in Hodgkin Disease

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<th>STAGE</th>
<th>FREEDOM FROM PROGRESSION (%)</th>
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*Note. Based on information from Ansell & Armitage, 2006.*
Recent Developments in Therapies

Monoclonal Antibodies

MOAB therapy has revolutionized the approach to treating B-cell lymphomas. Rituximab is a chimeric murine/human antibody. The use of rituximab has been extended to include most B-cell lymphomas that are CD20+, as well as many autoimmune diseases. The goal of some rituximab trials has been to improve activity by increasing the number of doses (McLaughlin et al., 1998) or by increasing the dose itself (O’Brien et al., 2001).

Maintenance dosing of rituximab also has been studied. Previously treated patients with indolent NHL were given four weekly doses of rituximab. All patients who responded were given maintenance doses of rituximab consisting of four weekly doses every six months for two years or until disease progression. The median progression-free survival was 34 months (Hainsworth et al., 2002). In a randomized rituximab study, time to progression was significantly longer in the group that received maintenance rituximab (Ghielmini et al., 2004).

The addition of rituximab to chemotherapy improved overall response rates in indolent and aggressive B-cell lymphomas. Two studies have suggested improved response rates in indolent lymphoma when rituximab was added to CHOP combination chemotherapy (Czuczman et al., 2004; Hiddemann et al., 2005). A trial by Marcus et al. (2005) reported an overall response rate and complete response rate to R-CVP (rituximab plus cyclophosphamide, vincristine, and prednisone) versus CVP alone as 81% and 40%, respectively, in the R-CVP arm and 57% and 10%, respectively, in the CVP arm. The median time to treatment for the R-CVP arm was 27 months compared to 7 months in the CVP arm. The studies support the use of rituximab with combination chemotherapy; as a result, rituximab has become standard therapy for first-line treatment in patients with indolent lymphoma.

The use of R-CHOP is widely established in DLBCL. A Groupe d’Etude des Lymphomes D’Adulte study by Coiffier et al. (2002) examined 197 older adults randomized to receive R-CHOP versus CHOP alone. The rate of response in the R-CHOP arm was 76% compared to 63% for the CHOP arm, and the R-CHOP arm showed prolonged event-free and overall survival. Toxicity was not increased when rituximab was added to combination chemotherapy.

Recent data support the use of rituximab for purging stem cells prior to autologous transplantation. Rituximab is used to eliminate stem cells that may contain lymphoma. The goal of rituximab is to prevent the reinfusion of disease stem cells back into patients with lymphoma (Corazzelli et al., 2006; Jacobsen & Freedman, 2004). In one study, rituximab was used as an in vivo purging agent in patients with follicular, mantle cell, and aggressive lymphoma before high-dose therapy. Stem cell harvests were negative for molecular markers in 9 of the 11 cases (Belhadj et al., 2004). Rituximab has been used in the setting of incompatible blood type in kidney transplantation, replacing plasmapheresis to remove anti-A or anti-B antibodies in some clinical settings (Jordon, Vo, Tyan, Nast, & Toyoda, 2005; Tyden et al., 2005).

Other MOABs are used in the treatment of NHL. Alemtuzumab (Campath®, Berlex, Montville, NJ) is a humanized MOAB directed against the CD52 antigen. The CD52 antigen is found on all lymphocytes (T and B cells), monocytes, macrophages, and eosinophils. Alemtuzumab has proven activity in CLL and T-cell lymphomas (Koening et al., 2002). Alemtuzumab has been studied in graft-versus-host disease in the allogeneic transplant population and may have a significant role in the future treatment and prevention of graft-versus-host disease (Delgado et al., 2006; Giralt, 2006).

Radioimmunotherapy

Radioimmunotherapy is a treatment option that has proven efficacy in patients who are rituximab refractory. It is a conjugated MOAB that is connected or joined with a radioisotope. It works to destroy the antibody present on B cells but also delivers radiation that causes a cross-fire effect, killing neighboring cells that may not express the CD20 antigen. The cross-fire effect can be seen in Figure 5. Selection criteria for radioimmunotherapy include bone marrow involvement less than 25%. Patients with a platelet count of less than 100,000 are not candidates. An absolute neutrophil count of 1,500 is required to safely administer radioimmunotherapy (Long & Versea, 2006).

In addition, two radioimmunonoconjugates are available commercially. Both are approved by the FDA for use in relapsed follicular lymphoma and transformed lymphoma. Y90 ibritumomab tiuxetan (Zevalin®, Biogen Idec, San Diego, CA) and 131I tositumomab (Bexxar®, GlaxoSmithKline, Research Triangle Park, NC) are the radioimmunotherapy agents currently in use. The radioactive dose is called the conjugated (or hot) dose, which always is preceded by the unconjugated (or cold) antibody dose.

Ibritumomab tiuxetan is a murine antibody and, when attached to yttrium, is a beta emitter. Rituximab (cold or unconjugated antibody) is given on day 1 followed by an indium-111 dose of ibritumomab for imaging. Scans are performed 48–72 hours after the ibritumomab infusion to ensure biodistribution. On day 7 or 8, rituximab is given again, followed by the radiated (conjugated or hot) dose of ibritumomab. In the pivotal trial of ibritumomab in a population that was refractory to rituximab, the response rate with ibritumomab was 74%, with 15% achieving complete remission (Witzig, Flinn, et al., 2002). In another study, patients with relapsed follicular lymphoma were randomized to receive rituximab or rituximab plus ibritumomab. Response rates in the rituximab plus ibritumomab arm were reported as 80% compared to 56% in the rituximab arm (Witzig, Gordon, et al., 2006).
al., 2002). The most significant adverse event was myelosuppression, which was seen five to eight weeks after treatment.

Tositumomab is attached to I131, which emits beta and gamma radiation. The treatment plan is similar to ibritumomab with a few exceptions. Radioimmunotherapy using I131 tositumomab is administered over seven to eight days. On day 1, tositumomab (cold or unconjugated antibody) is given followed by a radiolabeled dose of tositumomab, which is used for scanning. Scans are performed on days 0, 2–3, and 6–7 to ensure proper dosing. Monoclonal therapy is repeated in seven to eight days in a similar way, with the exception of the radioactive dose of ibritumomab. Potassium iodide is given 24 hours before the first dose of tositumomab to protect the thyroid. In a study by Kaminski et al. (2001), tositumomab was given to rituximab-refractory patients with a response rate of 63% and a complete remission rate of 29%. A more recent study by Kaminski et al. (2005) looked at patients with untreated follicular lymphoma who received one dose of radioimmunotherapy. The study reported a complete response rate of 75% and five-year progression-free survival rate of 59% for patients receiving one dose of radioimmunotherapy.

Implications for Nursing

Nurses must understand the pathophysiology of B-cell disorders and the treatment options associated with the diseases to provide the best possible care for patients. The use of MOABs in clinical practice is increasing at a very rapid pace. In an environment that is always changing, keeping up with emerging therapies can be difficult. However, nurses have many resources available to achieve the crucial goal of providing safe and comprehensive care to patients.

Knowledge of B-cell disorders can provide a foundation for nurses to improve patient assessment and to implement plans of care. Understanding the physiology of an infusion-related side effect will help nurses to better explain the information to patients and their families and will help patients cope with their experiences. The side effects can be distressing, but patients may feel that they have more control when side effects are explained with a scientific approach.

The significance of data surrounding monoclonal therapy is important for nurses to understand. The data are not always presented clearly, and many studies have limited practice applications because studies were small or differed in many ways. Nurses’ ability to interpret data is important for their patients and colleagues.

Monoclonal therapy is a relatively new concept in the treatment of many malignant and nonmalignant B-cell disorders. Knowledge of MOABs in these diseases will continue to grow. Nurses must continue to educate themselves and deliver accurate information to patients.

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