Non-Hodgkin lymphoma (NHL), a malignancy that manifests in the lymphatic system, is one of the most commonly occurring hematologic disease types in the United States and other Westernized countries. NHL is divided into a range of subtypes with differing clinical features and outcomes. Depending on the type of NHL and the patient’s overall clinical presentation, treatment varies from systemic combined chemotherapy regimens with or without immunotherapy, radioimmunotherapy, and transplants to investigational options. Oncology nurses play a vital role in implementing successful treatment and management of patients with NHL as oncology care moves into an era of novel targeted therapies.

Range of Non-Hodgkin Lymphoma Disorders

More than 30 types of NHL exist, and they are categorized by B, T, or natural killer cells. B-cell lymphomas comprise approximately 85% of all lymphomas. NHL can be indolent or aggressive; the cell type and subtype are used to determine an overall prognosis and the most appropriate course of treatment (see Figure 1). This article will focus on the most common lymphomas within the two groups and their treatment options. In addition, less well-known subtypes and investigational agents that may hold some benefit for indolent and aggressive subtypes will be explored (Wahl, 2005).

NHL is classified according to the World Health Organization (WHO) Revised European-American Lymphoma (REAL) system, which encompasses all lymphoma malignancies, including NHL, Hodgkin disease, and lymphoid leukemias (Akpek, Seifter, & Borowitz, 2000) (see Figure 2). The system uses four variables to determine an NHL subtype: cell morphology, immunophenotype, genetic features, and clinical situation.

Because NHLs are classified as indolent or aggressive, the inherent cellular growth of the lymphoid malignancy is used to define the particular classification. Figure 3 lists indolent and aggressive lymphomas. The Ann Arbor staging classification system is used to stage lymphomas and is based on the number of lymph nodes involved and organ involvement (Armitage, 2005) (see Table 1).

Indolent Lymphomas

Indolent or low-grade lymphomas are incurable with standard chemotherapy. The most common type of indolent lymphoma is follicular lymphoma, which accounts for approximately 22% of all NHLs worldwide and 35% of all NHLs in the United States. Median survival for patients with follicular lymphoma is 8–12 years (Peterson & Kahl, 2005).
Disease presentations in any type of lymphoma can vary. Many patients with follicular lymphoma are asymptomatic, whereas others may experience a gradual increase in B symptoms such as weight loss, night sweats, and daily fevers. Basic laboratory testing (i.e., complete blood count, lactic dehydrogenase (LDH), calcium, electrolytes, liver function tests, and renal function tests) should be obtained to assess the degree of disease activity. Diagnostic tests such as computed tomography or positron emission tomography scans can be used to identify lymphadenopathy. If lymphadenopathy is detected, a tissue biopsy should be performed. Follicular lymphoma appears as small cleaved cells that often are associated with a t(14;18) genetic rearrangement (Maloney, 2005). The immunophenotype of follicular lymphoma is cluster of differentiation (CD) 19, CD20, CD22 positive, and CD5 negative.

Once a tissue diagnosis has been made, treatment options are considered. Most patients present with advanced-stage disease (III or IV). Indolent lymphomas often are very treatable but not curable with standard therapy; therefore, when treatment should be initiated must be considered.

Treatment may be delayed for months or years depending on each patient’s individual scenario. In fact, patients with stage I diagnoses may be offered observation or localized radiation therapy. Stage I and II follicular lymphoma can be cured with radiation to the affected disease site. Alternatively, research supports that the initiation of treatment to patients with advanced-stage follicular lymphoma does not add to overall survival and warrants considering observation (Winter, Gascoyne, & Van Besien, 2004). Most patients in this situation may be monitored with blood work and computed tomography scans until symptoms or laboratory values suggest progressive disease such as splenomegaly, hepatomegaly, progressive lymphadenopathy, B symptoms, anemia, thrombocytopenia, or neutropenia.

The Follicular Lymphoma International Prognostic Index (FLIPI) is a performance tool that can help to determine a patient’s prognosis and determine when to initiate treatment (Solal-Celigny et al., 2004). The FLIPI uses five negative prognostic factors: age greater than 60 years, stage III or IV disease, hemoglobin level less than 12 g/dl, five or more nodal areas involved, and elevated LDH. One point is given for each prognostic factor identified. Patients with zero to one factor are considered low risk and have 5- and 10-year survival rates of 90% and 71%, respectively. Patients with two factors are at intermediate risk and have 5- and 10-year survival rates of 78% and 51%, respectively. Patients with high-risk disease have three to five factors and 5- and 10-year survival rates of 53% and 36%, respectively (Solal-Celigny et al.). Table 2 shows the FLIPI, which may help to determine which patients respond better to specific treatment regimens and can limit selection bias in clinical research studies.

Many chemotherapy regimens are available to treat patients with low-grade follicular lymphoma. Common chemotherapy regimens include CVP (cyclophosphamide, vincristine, and prednisone), CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), FCR (fludarabine, cytoxan, and rituximab), and chlorambucil. Rituximab (Rituxan®, Genentech, Inc., South San Francisco, CA), a monoclonal antibody that targets the surface antigen CD20 (found on more than 90% of B-cell NHLs [Hainsworth, 2000]) can be added to any of the previously mentioned treatment regimens. Relapsed disease can be treated with maintenance rituximab alone or a variation of any of the aforementioned therapies.
Indolent Types
- Follicular lymphoma
- Lymphoplasmacytic lymphoma
- Marginal zone B-cell lymphoma, mucosa-associated lymphoid tissue type
- Marginal zone B-cell lymphoma, nodal type
- Small lymphocytic lymphoma

Aggressive Types
- Anaplastic large cell lymphoma
- Burkitt-like lymphoma
- Burkitt lymphoma
- Diffuse large B-cell lymphoma
- Lymphoblastic lymphoma
- Mantle cell lymphoma
- Peripheral T-cell lymphoma
- Primary mediastinal large B-cell lymphoma

Figure 3. Non-Hodgkin Lymphoma: Indolent and Aggressive Types

Second- or third-line treatment considerations may include radioimmunotherapy (biritumomab [Zevalin®, Biogen Idec, San Diego, CA] or tositumomab [Bexxar®, GlaxoSmithKline, Research Triangle Park, NC]) or high-dose chemotherapy regimens followed by an autologous or allogeneic transplant. Investigational options, using agents such as proteasome inhibitors (bortezomib [Velcade®, Millennium Pharmaceuticals, Cambridge, MA]), antisense therapy, anti-BCL-2, oligonucleotides, and immunotherapy with idiotype vaccines, also should be considered.

Marginal Zone Lymphomas
Marginal zone lymphomas, which are indolent, can be divided into three types: splenic marginal zone B-cell lymphoma, extranodal marginal zone B-cell lymphoma (mucosa-associated lymphoid tissue [MALT]), and nodal marginal zone B-cell lymphoma. Marginal zone cells appear as small B lymphocytes with varied features that are dependent on the type of marginal zone. The immunophenotype of marginal zone lymphomas express CD19, CD20, and CD22 and are negative for CD5, CD10, and CD23 (Manson, 2006).

MALT lymphomas often occur in the stomach and commonly are associated with Helicobacter pylori, which frequently is treated with antibiotics, histamine receptor-type 2 blockers, and proton pump inhibitor coverage (Manson, 2006). Treatment of MALT lymphomas found in the lungs, thyroid, breasts, lacrimal glands, and salivary glands is similar to treatment of follicular lymphoma and can include radiation therapy or combination systemic chemotherapy.

Aggressive Non-Hodgkin Lymphoma
Clinically aggressive lymphomas are defined in the WHO REAL classification for lymphoid neoplasms as diffuse large B-cell lymphoma, peripheral T-cell lymphoma, anaplastic large cell lymphoma, and lymphoblastic lymphoma (Akpek et al., 2000). The most common type of aggressive NHL is diffuse large B-cell lymphoma, which encompasses 32% of the disease subset worldwide (Coifier, 1998). Aggressive NHL is curable, but patients typically present with symptoms that require urgent treatment. The International Prognostic Index (IPI) score is used to determine the most effective treatment options for aggressive NHLs only (Armitage, 2005) (see Table 3). The major differences between the IPI and FLIPI are the inclusion of anemia as a prognostic factor in the FLIPI and the overall percentage of predicted responses between the two histologies (i.e., follicular NHL and aggressive NHL). According to the IPI, low-risk patients with aggressive lymphomas have a five-year survival rate of 73%. In patients at high risk, the five-year survival rate drops to 26% (Marcus, 2003).

Patients with localized, nonbulky diffuse large B-cell lymphoma represent 30% of the disease subset and can be cured with standard rituximab plus CHOP (R-CHOP) chemotherapy, using three 21-day treatment courses plus localized radiation therapy (Marcus, 2003). Patients also may be treated with six to eight cycles of R-CHOP alone to limit complications associated with radiation. Both treatment regimens are acceptable with the overall intent to cure.

Patients diagnosed with advanced-stage diffuse large B-cell lymphoma are treated with standard R-CHOP for six to eight cycles. Patients should be monitored closely, with frequent diagnostic imaging, laboratory evaluations, and physical examinations. Patients with high-risk disease may be considered for aggressive therapy after relapsed diffuse large B-cell lymphoma with high-dose chemotherapy regimens followed by autologous stem cell transplantation. Some of the chemotherapy regimens are DICE (dexamethasone, ifosphamide, cisplatin, and etoposide), ESHAP (etoposide, methylprednisolone, cisplatin, and cytarabine), and EPOCH (doxorubicin, vincristine, etoposide, cyclophosphamide, and prednisone) (Dobashi et al., 1998).

Patients with chemotherapy-responsive disease experience better overall response and survival rates compared to those who are not responsive to salvage chemotherapy (Steingass, 2006). Relapsed disease can pose a difficult situation because chemotherapy resistance is common and limited effective treatment options exist; therefore, patients may pursue investigational therapies in an attempt to control the disease and its associated symptoms.

Mantle Cell Non-Hodgkin Lymphoma
Mantle cell lymphoma comprises a distinct subset of aggressive lymphomas. Accounting for approximately 5%–8% of all NHLs, patients with mantle cell lymphoma typically have a poor prognosis with standard therapy (Marcus, 2003). Mantle

<table>
<thead>
<tr>
<th>Table 1. Ann Arbor Staging</th>
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<tr>
<td>STAGE</td>
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<tr>
<td>I</td>
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<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
</tr>
</tbody>
</table>

Note. Patients’ disease staging includes the following: A (a presence of systemic symptoms), B (without systemic symptoms), E (extranodal organ involvement), or S (presence of systemic disease).

Note. Based on information from Armitage, 2005.
cells may appear as atypical small lymphoid cells with irregular, indented nuclei. The immunophenotype expresses CD19, CD20, CD22, and CD10 but is negative for CD23 (Hiddemann et al., 2005). Most patients with mantle cell lymphoma present with advanced-stage disease, including bone marrow involvement, and require therapy immediately to control their symptoms. Unfortunately, relapsed disease and chemotherapy resistance are common. Standard therapy includes R-CHOP or high-dose HYPER-CVAD chemotherapy. (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone). Hyperfractionated cyclophosphamide is dose-intensive treatment in which small, frequent doses are administered over time rather than one bolus infusion (Kantarjian et al., 2004). Clinical trials should almost always be considered for patients with mantle cell lymphoma because of its incurable prognosis.

**Burkitt Lymphoma**

Burkitt lymphoma is considered a highly aggressive lymphoma. First discovered in African children in the 1950s, the disease is associated with the Epstein-Barr virus (Goldstein & Bernstein, 1990). Its identifying cells appear as small cells that are non-cleaved. Burkitt lymphoma cells divide rapidly with frequent mitotic figures. Patients with limited disease have an excellent prognosis (Divine et al., 2005). The overall survival rate ranges from 50%–70%, although when central nervous system or bone marrow involvement is present, long-term survival is reduced to less than 30% (Divine et al.). The immunophenotypes of Burkitt lymphoma are the expression of CD19, CD20, CD22, and CD10 and typically are CD5 and CD23 negative. Treatment consists of an intense chemotherapy regimen of CODOX (cyclophosphamide, doxorubicin, vincristine, methotrexate IV, and intrathecal administration of cytarabine and methotrexate) for cycles 1 and 3 alternating with cycles of IVAC (ifosfamide, etoposide, cytarabine IV, and intrathecal methotrexate) for cycles 2 and 4.

**Treatment Options**

**Chemotherapy**

Chemotherapy is the most widely used treatment option in patients with NHL. Regimens include single-agent and combination therapy. The appropriate chemotherapy is determined by many factors, including type of NHL, comorbidities, patient choice, and physician preference. Patients who have relapsed from initial therapy usually are treated with a combination regimen or agent that they have not received previously. Monoclonal antibodies often are added to various chemotherapy regimens for synergistic purposes. See Figure 4 for common NHL treatment regimens.

**Monoclonal Antibodies**

Monoclonal antibodies have been used in the treatment of lymphomas since the approval of rituximab by the U.S. Food and Drug Administration (FDA) in 1997 (Hainsworth, 2000). The anti-CD20 monoclonal antibody rituximab is a bioengineered protein or chimeric (combined antibody) consisting of a murine (mouse-based) variable region fused to a human constant region. Rituximab is approved by the FDA for use in relapsed or refractory follicular or transformed NHL (Genentech, Inc., 2006). Treatment-related side effects typically are well tolerated and often are reversible.

Retreatment with rituximab on a maintenance schedule is becoming increasingly more common because of effective treatment outcomes. Maintenance dosing has been studied in two large randomized studies (Ghielmini et al., 2004; Hainsworth et al., 2002). Hainsworth et al. studied 62 patients with previously untreated indolent NHL who received maintenance rituximab. Standard-dose therapy (375 mg/m²) was administered weekly for four weeks every six months for two years. The researchers reported an overall response rate of 74% and a complete response rate of 57%. The time to progression ranged from 34–52 months, depending on the indolent lymphoma subtype (Hainsworth et al.). Alternatively, Ghielmini et al. compared a

### Table 2. Follicular Lymphoma International Prognostic Index

<table>
<thead>
<tr>
<th>RISK GROUP</th>
<th>NUMBER OF FACTORS</th>
<th>DISTRIBUTION OF PATIENTS, %</th>
<th>5-YEAR OS, % (SE)</th>
<th>10-YEAR OS, % (SE)</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0–1</td>
<td>36</td>
<td>90.6 (1.2)</td>
<td>70.7 (2.7)</td>
<td>1.0</td>
<td>NA</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
<td>37</td>
<td>77.6 (1.6)</td>
<td>50.9 (2.7)</td>
<td>2.3</td>
<td>1.9–2.8</td>
</tr>
<tr>
<td>High</td>
<td>≥3</td>
<td>27</td>
<td>52.5 (2.3)</td>
<td>35.5 (2.8)</td>
<td>4.3</td>
<td>3.5–5.3</td>
</tr>
</tbody>
</table>

N = 1,795. OS indicates overall survival; SE, standard error; CI, confidence interval; RR, relative risk (of death); and NA, not applicable.

* Factors adversely affecting survival in the Follicular Lymphoma International Prognostic Index include age greater than 60 years, Ann Arbor stage III–IV, number of nodal sites greater than 4, serum lactate dehydrogenase level greater than the upper limit of normal, and hemoglobin level less than 120 g/l.


### Table 3. International Prognostic Index

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>FAVORABLE (0 POINTS)</th>
<th>UNFAVORABLE (1 POINT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>≤ 60</td>
<td>&gt; 60</td>
</tr>
<tr>
<td>Tumor stage</td>
<td>I or II (localized)</td>
<td>III or IV (advanced)</td>
</tr>
<tr>
<td>Number of extranodal sites</td>
<td>≤ 1</td>
<td>&gt; 1</td>
</tr>
<tr>
<td>Performance status</td>
<td>0 or 1</td>
<td>≥ 2</td>
</tr>
<tr>
<td>Serum lactate dehydrogenase</td>
<td>Normal</td>
<td>Abnormal</td>
</tr>
</tbody>
</table>

Note. Based on information from Marcus, 2003.
single course of rituximab with extended therapy in previously treated and untreated patients. All patients were treated with standard induction therapy of rituximab weekly for four weeks and were reassessed for response after the initial four weeks. Patients who did not progress were randomized to receive either extended rituximab (one dose at three, five, seven, and nine months for a total of four doses) or no further treatment. The primary end point was event-free survival (i.e., freedom from disease progression or relapse, initiation of new treatment, or death), which was reported as 22.4 months in the group receiving extended therapy compared with 13.6 months in the group receiving one-time treatment. As a result, extended rituximab therapy was proven effective (Ghielmini et al.).

**Radioimmunotherapy**

Radioimmunotherapy is the addition of radioisotopes to anti-CD20 antibodies in relapsed or refractory follicular lymphoma and transformed patients (i.e., those whose disease has changed from having low-grade features to an aggressive disease component). The two approved radioimmunotherapy agents are iodine 131 or tositumomab (Bexxar) and ibritumomab tiuxetan (Zevalin). Both agents are administered on an outpatient basis in which patients receive two doses approximately one week apart. Radiation emission varies between the two agents. Ibritumomab tiuxetan is a pure beta emitter, and tositumomab is a beta and a gamma emitter. The most common and major toxicity associated with both agents is myelosuppression, which is a delayed, reversible occurrence.

Proper patient selection is crucial when delivering radioimmunotherapy. Eligible patients should have no more than 25% lymphoma in the bone marrow and should have a reasonably healthy bone marrow reserve, with overall cellularity greater than 15%. In addition, a circulating platelet count of more than 100,000/mm³ and an absolute neutrophil count of more than 1,500/mm³ are required for baseline treatment consideration (Cheson, 2005).

Witzig, Gordon, et al. (2002) randomized 143 patients with relapsed or refractory low-grade, follicular, or transformed CD20+ lymphoma to receive either yttrium 90 ibritumomab or rituximab. The overall response rate was 80% for the yttrium 90 group versus 56% for the rituximab arm. The median duration of response was similar in the two groups (14.2 versus 12.1 months). Yttrium 90 ibritumomab has shown efficacy in rituximab-refractory patients with an overall response rate of 74%, a complete response rate of 15%, and a partial response rate of 59% (Witzig, Flinn, et al., 2002).

The iodine 131 anti-CD20 antibody tositumomab seems to have a similar response rate to yttrium 90. A multicenter phase II study of 45 patients demonstrated an overall response rate of 57% (Kaminski et al., 2001). In the pivotal trial for tositumomab, all 60 patients had been treated with at least two prior chemotherapy regimens and relapsed within the last six months of their last qualifying chemotherapy regimen. The overall response rate was 65% in comparison to patients’ last chemotherapy regimen. The median duration of response was 6.5 months versus 3.4 months (Kaminski et al., 2001).

First-line treatment with radioimmunotherapy, given its high response rates and durability, has increasing promise. Kaminski et al. (2005) published treatment responses for upfront therapy, eliminating chemotherapy altogether. Seventy-six patients with follicular lymphoma were treated with iodine 131 tositumomab, with an overall response rate of 95% and a 75% complete response rate. Median progression-free survival was 6.1 years.

**Immunotherapy**

Vaccine therapy in NHL currently is under investigation for patients with relapsed low-grade and aggressive NHL. Immunotherapy uses healthy B cells that express an immunoglobulin with a unique heavy and light chain variability sequence. The sequences allow for an antigen-binding site to form and are an ideal medium for vaccines and antibodies to be implemented. Results from various trials have demonstrated that patients who mount a response to a custom-made vaccine composed of a tumor-idiotype protein attached to an immune adjuvant (keyhole limpet hemocyanin) have extended disease-free responses versus those who do not mount an immune response (7.9 versus 1.3 years, respectively) (Hsu et al., 1997). Most of the patients who responded to the custom-made vaccine had follicular or low-grade NHL and received initial induction chemotherapy. In addition, Timmerman et al. (2002) vaccinated 35 patients with dendritic cells pulsed with tumor-derived idiotype proteins. Of the 23 patients who completed the vaccination schedule, 15 mounted an immune response. At a median of 43 months after chemotherapy, 16 of the 23 patients showed no tumor progression. Six patients who progressed were eligible for a booster injection series and showed a response (Ganti et al., 2005). Currently, two large randomized trials are assessing the role of vaccines in follicular lymphoma, and the results are highly anticipated. Both trials are exploring the most appropriate time to initiate vaccine therapy in the treatment course (initially or after chemotherapy completion). The results remain unavailable.

**Proteasome Inhibitors**

Proteasome inhibitors are a new class of drugs for the treatment of NHL. Bortezomib (Velcade) is the most commonly used proteasome inhibitor in this class of drugs, which inhibit a large protein complex known as a proteasome. Proteasomes are responsible for maintaining protein concentrations in cells and have a unique ability to interrupt an abnormal accumulation of
Disease-related proteins. Bortezomib has been approved for use in patients with relapsed multiple myeloma. The drug has been studied in patients with NHL as a single agent or in combination with chemotherapy, but its effectiveness has been controversial. Multicenter data noted a 60% overall response rate in patients with follicular NHL (O’Connor et al., 2004). Alternatively, Goy et al. (2005) reported objective responses in only 13% of patients. To explain the data discrepancies, identifiable differences in the studies were noted. Patients not experiencing an objective response by cycle 4 in Goy et al.’s study were taken off the protocol therapy, whereas in O’Connor et al.’s trial, therapy was continued until disease progression or unacceptable toxicity was experienced. Both studies reported slow responses in various indolent NHL subtypes. For example, patients with mantle cell lymphoma responded more quickly than patients with follicular NHL (5 weeks versus 11 weeks) (Goy et al.). The results of the trials have significant implications in terms of specific disease responses, duration of treatment, and cessation of bortezomib therapy. Studies with single agents and combined therapy are ongoing to assess when bortezomib is most effective.

Transplant

Transplant options in patients with NHL vary according to subtype. Patients with indolent NHL who have failed chemotherapy and monoclonal antibody combinations may be offered high-dose chemotherapy followed by autologous or allogeneic stem cell transplantation. In an aggressive treatment setting, autologous transplants often are considered once standard therapy has failed. In patients with relapsed aggressive disease who have received high-dose chemotherapy or a combination of chemotherapy and radiation therapy, long-term survival has been induced in 10%–50% of patients (Steingass, 2006).

The advantages of transplantation include the durability of responses and the potential for increased survival. Disadvantages include immediate and long-term toxicities, with a potential for disease recurrence (Winter et al., 2004). A more comprehensive review of transplants in various NHL subtypes is covered by Amy Goodrich, CRNP, in “Emerging Therapeutic Options for the B-Cell Disorders” in this supplement.

Investigational Options

Monoclonal antibodies: Success with commonly known NHL antibodies has led to new possibilities. Epratuzumab (IMMU-103, LymphoCide™, Immunomedics, Inc., Morris Plains, NJ), a humanized anti-CD22 monoclonal antibody, is under investigation. Leonard et al. (2003) treated 55 patients with relapsed follicular NHL with epratuzumab and noted an objective response of 24%. Postema et al. (2005) combined epratuzumab with the radioisotope rhenium Re-186 in a phase I study and determined that a single dose of 2.0 gigabecquerel/m2 was well tolerated, with 5 out of 15 objective responses in a diverse NHL histology population. Apolizumab (Remitogen™, Protein Design Labs, Fremont, CA) is a humanized monoclonal antibody that binds to a variant of the HLA-DRB chain (Gingrich, Dahle, Hoskins, & Senneff, 1990) and is effective in cell-mediated cytotoxicity and complement-mediated lysis (Press, Leonard, Coiffier, Levy, & Timmerman, 2001). In their phase I study, Link et al. (2001) treated 20 patients with apolizumab. Clear evidence of antitumor activity was identified, especially in follicular lymphoma, and toxicities were primarily grade I and II.

Galiximab® (Biogen Idec), a chimeric antibody directed against CD80, is showing some promise in hematologic malignancies. Czuczman et al. (2005) conducted a phase I/II study in patients with relapsed and refractory follicular NHL. The drug was well tolerated and had limited toxicities. The researchers observed two complete responses and one partial response in 34 evaluable patients.

Cpg oligonucleotides: Cpg oligonucleotides activate immune cell subsets, including those that act in cell-mediated cytotoxicity, and may act synergistically with the effects of monoclonal antibodies. To demonstrate the effect, Friedberg et al. (2005) conducted a phase I study combining escalating doses of immunostimulatory Cpg oligonucleotide (1018ISS) with rituximab in 16 patients with relapsed, refractory NHL. The regimen was tolerated without any major adverse effects. One complete response, five partial responses, and two progressive disease responses were noted. Interestingly, correlative studies identified that Cpg administration was associated with a dose-related increase in expression of several interferon-induced genes (Friedberg et al.).

Antisense therapy: The bcl-2 gene commonly is overexpressed in patients with NHL; in fact, more than 85% of patients with follicular NHL overexpress bcl-2, which leads to apoptosis resistance and disease growth. Waters et al. (2000) conducted a phase I study of antisense therapy in 21 patients with NHL. One complete response, two partial responses, nine patients with stable disease, and no cases of progressive disease were reported (Waters et al.). The study confirmed that antisense therapy alone has activity in NHL. Combined therapy with chemotherapy currently is under investigation.

Nursing Implications

Effective nursing strategies for patients with NHL are critical to successful care. Nurses are at the forefront of effective treatment-related symptom management. Their roles as acute observers and educators are hallmarks of valuable nursing care. Oncology nurses must be aware of the common side effects associated with NHL treatments so that they are able to eliminate or reduce treatment-related complications.

Myelosuppression

Myelosuppression is the most common lymphoma treatment-related side effect and is seen with many chemotherapy regimens, particularly those that include alkylating agents, anthracyclines, and purine analogs. Radioimmunotherapy agents can cause myelosuppression, but it typically is a delayed observation and occurs one to two months after completion of treatment. Patients often become familiar with the “trends” of their blood counts and should be encouraged to be aware of associated side effects (e.g., shortness of breath with anemia). Early interventions are critical to prevent more serious complications, such as the need for growth factor injections with anemia or thrombocytopenia. Patient and caregiver education can be very effective in preventing complications associated with low blood counts. For example, maintaining neutropenic precautions and using...
good hand-washing techniques can prevent the occurrence of serious infections.

**Gastrointestinal Effects**

Nausea, vomiting, and diarrhea are the most common gastrointestinal side effects seen in the treatment of patients with NHL. Most of the side effects are manageable with effective antiemetic coverage in various categories (e.g., 5HT₃ antagonists, dopamine agonists). Combining antiemetic regimens with steroids and antianxiety medications may add to the effectiveness of single-medication regimens. Diarrhea can be prevented with effective antidiarrhea medications such as loperamide. Hydration should be encouraged to eliminate the potential for dehydration, electrolyte abnormalities, and nutritional deficiencies. Progressive gastrointestinal symptoms that are not responsive to early interventions should be investigated further to evaluate and prevent more advanced complications.

**Alopecia**

Alopecia can be a devastating side effect of therapy, especially with alkylating and anthracycline medications or even radiation therapy. Nurses must provide supportive services and referrals for cranial prostheses through organizations such as the American Cancer Society.

**Mucositis**

Mucositis often is associated with chemotherapy and radiation treatments. Oral mucositis is a dose-limiting side effect of cancer therapy. Depending on the type of treatment used (chemotherapy, radiation therapy, or bone marrow transplant), as many as 90% of patients can develop mucositis (McGuire, Rubenstein, & Peterson, 2004). The side effect can be managed with combinations of topical lidocaine preparations and pain medications. Mucositis can be correlated with low blood counts, so nurses should be proactive with patients who may not exhibit signs of an eruption. Patients should be encouraged to avoid spicy, acidic, or fried foods to help alleviate exacerbation.

**Infusion-Related Side Effects**

Infusion-related side effects often are seen with monoclonal antibody therapy; however, they also can occur with some chemotherapy medications such as taxanes. Premedicating patients with steroids, acetaminophen, or antihistamines may prevent a reaction. However, if a severe reaction occurs, treatment should be interrupted and the symptoms should be treated before attempting to rechallenge the patient.

**Considerations After Radioimmunotherapy**

Because radioimmunotherapy is an outpatient procedure that is completed over a single two-week course, nurses must provide patients with comprehensive instructions that vary depending on the radioisotope being used (beta emitter versus gamma emitter). For example, specific patient instructions exist for ibritumomab tiuxetan. Universal precautions should be used for the first three days after treatment regarding body fluids. Good hand washing should be maintained at all times but particularly during the first week after treatment completion. Barrier precautions should be maintained during sexual intercourse for as long as one year after treatment (Byar, 2004).

Because tositumomab is a beta and gamma emitter, patients receive medications before and after treatment to protect against the development of thyroid abnormalities. For four to seven days, patients are instructed to sleep alone in a separate bed. In addition, patients should maintain a distance of at least six feet from children and pregnant women and limit exposure to others when traveling via car. Patients’ laundry must be washed separately, and sexual contact should be avoided for at least four to seven days after tositumomab administration (International Commission on Radiological Protection, 2004). Ibritumomab tiuxetan and tositumomab require hematologic supportive care for as long as three months after treatment.

**Vaccine Therapy Considerations**

Vaccine therapy currently is available only in clinical trials. Most vaccines are given to outpatients as subcutaneous or intramuscular injections. The vaccines usually are administered as a series, meaning that they may be given every several weeks and that the total number of injections can vary. The vaccine injection typically is followed by a booster immunologic injection for several days in a row. The immune stimulants allow for the immune system to be turned on. Granulocyte macrophage–colony-stimulating factor (GM-CSF) is used most commonly and is injected at the same site as the vaccine. Common side effects associated with vaccine injections and GM-CSF are flulike symptoms, injection site erythema, edema, and pruritis. Some patients may experience localized injection site discomfort over time with generalized fatigue and myalgias. Because vaccines and GM-CSF are administered almost simultaneously, identifying which drug causes symptoms is difficult. Over-the-counter medications such as acetaminophen, antihistamines, and nonsteroidal medications are effective in alleviating or reducing some of the common symptoms associated with vaccine therapy. Topical and oral steroid use usually is prohibited because it may interfere with the effectiveness of vaccine therapy (Hohenstein, King, Fiore, O’Brien, & Blumel, 2005).

**Summary**

NHL is a complex disease with multiple symptoms and numerous treatment options. Continued advances in the treatment of different NHL subtypes are expanding and hold promise. Clinical trials are critical to the potential for cure and should be explored when considering treatment options. Oncology nurses play a vital role in the successful treatment and management of patients with NHL as they move into an era of novel targeted therapies.

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