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OBJECTIVES:

To review the etiology, epidemiology, classification, prognosis, diagnosis, and nursing implications of non-Hodgkin's lymphoma

DATA SOURCES:

Research studies, review articles, and book chapters pertaining to non-Hodgkin's lymphoma.

CONCLUSIONS:

Non-Hodgkin's lymphomas are a heterogeneous group of lymphoproliferative disorders, increasing in frequency, for which therapy ranges from supportive to curative.

IMPLICATIONS FOR NURSING PRACTICE:

An understanding of the variety of presentations and treatments of non-Hodgkin's lymphomas will enable the oncology nurse to assist patients and their families to cope with the disease, make treatment-related decisions, and optimize the patient's quality of life.

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NON-HODGKIN'S LYMPHOMA

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THE non-Hodgkin's lymphomas (NHLs) are a diverse group of malignancies with a common origin in lymphoid cells. They are heterogeneous in clinical behavior, morphologic appearance, cellular origin, etiology, and pathogenesis.[1] The American Cancer Society estimates that in 1998 there will be 55,400 new cases of NHL and 24,900 related deaths in the United States.[2]

EPIDEMIOLOGY

Between 1973 and 1991 there was a 73% increase in the incidence of NHL, one of the largest among the major cancer sites. Part of this increase has been attributed to the acquired immunodeficiency syndrome (AIDS). Non-Hodgkin's lymphoma is approximately 60 times more common in persons with AIDS than the general United States population, but AIDS alone cannot explain the increase in NHL that began years before the AIDS epidemic surfaced and that continues in the absence of human immunodeficiency virus infection.[3]

Non-Hodgkin's lymphoma is the sixth most common cause of cancer-related deaths in the United States. It is more prevalent in males than females, and the incidence is higher in whites than blacks. Survival outcomes are better for women than men, and for persons younger than 65 years of age. There is a steady, age-dependent increase from childhood through the eighth decade of life. Because the average age at diagnosis is the fifth decade, the resultant number of years of life lost to these diseases ranks NHL fourth in economic impact among cancers in the United States.[4,5]

ETIOLOGY

The incidence of NHL has risen inexplicably. Research is needed to determine possible causes. No hereditary pattern has been identified, nor have any ethnic or dietary risk factors been specifically linked. No common etiologic agent can be associated with all cases of NHL.[6] An increased risk is associated with a variety of immunodeficiency states, autoimmune disorders, and infectious, physical, and chemical agents; these are identified in Table 1.

TABLE 1. Etiologic Agents Associated With Increased Risk of Non-Hodgkin's Lymphoma

Genetic	Immunologic	Infectious	Environmental
Chromosomal translocations[7] Oncogenes (c-*myc*, c-*bcl*-2, mutant p53)[7]	Congenital and acquired immunodeficiencies[4] Autoimmune disorders with chronic inflammation[4]: Hashimoto'sthyroiditis, Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus Hodgkin's disease treated with chemotherapy and radiation[5] Renal allografts[5]	Epstein-Barrvirus[4-8] Human T-cell leukemia/lymphoma virus-1[7] Human herpes virus-8 (KSHV-8)[7,9] *Helicobacter pylori*[4,10]	Pesticides (herbicides, fungicides, insecticides)[3,5,11] Occupational exposure to organic solvents[3,5] Dark, permanent hair dyes[3,5,12,13]

CLASSIFICATION

The classification of NHL has evolved steadily throughout the 20th century. Terminology is complex, inconsistent, and ambiguous. As noted by Willis 50 years ago "nowhere in pathology has a chaos of names so clouded clear concepts as in the subject of lymphoid tumors."[14]

A classification system for NHL should (1) allow the definition of distinct subgroups to establish a proper diagnosis, (2) be clinically useful, (3) enable clinicians to estimate the prognostic relevance, and (4) guide therapeutic decisions.[15] Thus, as insight into the pathogenesis of NHL changes, the classification system must be reviewed and updated.

The Rappaport classification system, first proposed in 1956, was largely descriptive and based on histologic and cytologic characteristics of the cells. Lymphomas were divided according to architectural pattern: nodular or diffuse. Small cells were termed "lymphocytic," large cells were called "histiocytic," and intermediate-sized cells lacking evidence of lymphoid or histiocytic origin were called "undifferentiated." "Mixed lymphomas" were combinations of small and large cells. Cells similar in size and morphology to normal lymphocytes were "well-differentiated" and those of irregular shape were "poorly differentiated.'' The Rappaport terminology has been widely used in the Surveillance, Epidemiology and End Results program data base.[1,4,15]

Based on expanding knowledge of lymphatic system physiology and immunology, six distinct classification systems evolved worldwide in the 1970s. Consequently, it became difficult to compare results obtained in different clinical trials. The Lukes and Collins classification and the Kiel classification (KC) are best known. The Lukes and Collins classification system used B- and T-cell phenotypes as its basis, and attempted to relate malignant lymphomas to their normal counterparts within the lymphatic system. The KC system defined NHL on the basis of morphologic and immunologic criteria; it divided NHL into two main groupings: high-grade (aggressive) and low-grade (indolent) malignancies based on their cytologic features, not survival.[1,15-17]

The National Cancer Institute funded a study to compare the major classifications in the early 1980s. An examination of 1,175 lymphoma cases revealed that all six could identify tumors of low- or high-grade behavior. No one scheme was significantly better than another. The researchers proposed a "working formulation'' based on clinical parameters and morphology. Lymphomas were grouped according to their natural history, response to therapy, and overall survival. The subtypes were identified with alphabetical letters (A to J) and grouped into three clinical prognostic groups (low, intermediate, and high grades). At the time of publication, the Working Formulation (WF) investigators stated that it was "not proposed as a new classification system but as a means of translation among the various systems.'' However, this distinction has not always been appreciated.[1,4,16]

Ultimately, the WF became the main classification system in the United States and the KC achieved prominence in Europe. This situation has complicated transatlantic communication and interpretation of published studies because the

WF categories are designed according to cell size and survival, whereas the KC system reflects the physiopathology of the lymphoid tissue and does not always correlate with clinical behavior.[17,18]

This frustration, and the recognition of several new lymphoma entities in recent decades, raised the question of whether it was time for a new lymphoma classification system. In 1991, 19 hematopathologists from Europe, the United States, and Asia founded the International Lymphoma Study Group. Joint work revealed that despite different terminology, the ILSG members agreed on a large number of distinct lymphoma entities. Some were easily recognized; others were prone to subjective variability. For this reason, the International Lymphoma Study Group concluded that a lymphoma classification system should simply be a list of well-defined "real" disease entities. Cases that do not fit into one of the defined entities should be left unclassified, reflecting the fact that everything about lymphomas and the immune system is not yet understood. This Revised European-American Lymphoma (REAL) classification was proposed in 1994. The REAL system includes all lymphoma types and the extranodal lymphomas that were not included in the other systems. It corresponds in many aspects to the KC because of its biologically oriented approach. Studies aimed at facilitating the translation of the REAL into clinically useful prognostic groupings are ongoing. The goal is an internationally agreed on approach to lymphoma classification.[14-20] Table 2 compares the WF, the KC, and the REAL classification systems.[15]

DIAGNOSTIC EVALUATION

The initial approach to the patient with uncertain lymphadenopathy first involves a high

TABLE 2. Summary of NHL Classification Systems

WF	REAL B-Cell Neoplasms*	REAL T-Cell Neoplasms*	KC
A: Small lymphocytic, plasmacytoid	B-cell CLUSLUPU mantle cell; lymphoplacytoid	T-cell CLUPLL; LGL; lymphoplasmacytoid	B- and T-cell CLL/PLL; lymphoplasmacytoid immunocytoma
B: Follicular, predominantly small cleaved cell	Mantle zone; marginal zone; follicular center, follicular grade 1		Centroblastic/centrocytic, follicular
C: Follicular, mixed small cleaved and large cell	Follicular center; follicular, grade II; marginal zone/MALT		Centroblastic/centrocytic, follicular
D: Follicular, large cell	Follicle center; follicular, grade III		Centroblastic, follicular
E: Diffuse, small cleaved cell	Mantle cell; follicle center, diffuse small cell; marginal zone/MALT	Peripheral T-cell, unspecified; mycosis fungoides/Sezary syndrome; adult T-cell lymphoma/leukemia	Mycosis fungoides/Sezary cell syndrome; pleomorphic, small T-cell; centrocytic; centroblastic/centrocytic, diffuse
F: Diffuse, mixed small and large cell	Marginal zone/MALT; mantle cell	Peripheral T-cell, unspecified; angiocentic; angioimmunoblastic	T-cell angioimmunoblastic; pleomorphic medium and large T-cell; lymphoepithelioid
G: Diffuse, large cell	Diffuse large B cell	Peripheral T-cell, unspecified	Centroblastic; pleomorphic T-cell
H: Large cell immunoblastic	Diffuse large B cell	Peripheral T-cell, unspecified; intestinal T-cell	B- and T-cell immunoblastic; B- and T-cell large cell anaplastic
I: Lymphoblastic	B-precursor lymphoblastic	Precursor T-lymphoblastic	B and T-cell lymphoblastic
J: Small noncleaved cell Burkitt's, non-Burkitt's	Burkitt's; high-grade B-cell, Burkitt-like		Burkitt's lymphoma

Abbreviations: CLL, chronic lymphocytic leukemia; LGL, large granular lymphocytic leukemia; MALT, mucosa-associated lymphoid tissue; PLL, prolymphocytic leukemia; SLL, small lymphocytic lymphoma.
*Some disease entities and variant forms have been omitted for clarity. Duplication of some entities is present for comparison with WF categories.
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index of suspicion combined with a systematic evaluation. While the appearance of an enlarged lymph node in the absence of infection may cause alarm, it is important to note that up to 56%of healthy adults may exhibit cervical adenopathy[21]; a study of healthy college students found not only adenopathy, but also splenomegaly.[22] Certainly, any enlargement of the nodes warrants follow-up evaluations to document regression or further pathology.

As with any new complaint, the work-up begins with a thorough history and physical examination. Complete blood cell count, erythrocyte sedimentation rate, and peripheral blood smear are performed to rule out other causes of lymphadenopathy, such as infectious mononucleosis. Blood cultures and other serologic studies for viral and autoimmune disease provide important differential information. Chemistries, especially lactate dehydrogenase, are performed, as elevated lactate dehydrogenase may be seen in advanced NHL, and is considered a poor prognostic factor.[23] Recent localized infectious processes or other illnesses, as well as home and occupational exposure to carcinogens are evaluated.

On examination, lymph nodes involved in infectious processes are generally tender and possibly painful, whereas lymphomatous nodes tend to appear firm and rubbery and are found in generalized patterns. Carcinomatous nodes are often hard and sometimes matted to one another or fixed to underlying structures in contiguous or regional patterns.[24] Other hallmarks of lymphoma such as systemic B symptoms are seen in approximately 20% to 30% of patients, but also may be found in other disease states, such as certain infections, connective tissue diseases, and angioimmunoblastic lymphadenopathy.[25]

When used discriminantly, lymph node biopsy specimens are an important part of the diagnostic process. Indications include adenopathy persisting for longer than 3 weeks which progresses in size or spreads to further areas, B symptoms that cannot be attributed to other causes, abnormal blood testing, or radiography indicating possible extranodal presentation. Additionally, due to the aggressive nature of AIDS-related NHL, any symptomatic patient at increased risk for or known to be positive for the human immunodeficiency virus should undergo biopsy to rule out high-grade lymphoma.[25]

STAGING

Once the diagnosis of NHL is made and the histology or cell type causing the disease has been determined, it is necessary to gauge the amount and location of lesions throughout the patient's body, or to stage. Historically, the exploratory laparotomy, with the surgeon responsible for palpation of organs and lymph node chains to uncover disease, was the "gold standard." Later, lymphangiography became important in discerning levels of involvement within the lymph system. However, because of the clarity of results, it has been generally supplanted by the use of computerized tomography, except when structural intranodal changes must be evaluated.[26] Since the advent of non-invasive imaging techniques, computed tomography and magnetic resonance imaging studies have been usefully applied to the initial staging of NHL and they represent today's standards.

To further determine the presence and extent of extranodal involvement, renal and liver function tests are performed. Bilateral bone marrow biopsies and aspirates are essential as spread to the marrow is common, especially in low-grade disease.[27]

To organize all these clinical data, the Ann Arbor staging system was initially developed in 1971 to describe the amount and location of disease in Hodgkin's disease patients.[28] It consists of four major stages that elucidate the presence of certain symptoms or sites of presentation. The later adaptation of the system to accommodate the staging of NHL is not precise in that some of the important prognostic implications in the system as illustrated by Hodgkin's disease are lost, and the capacity to describe bulky disease and other factors is not included. Table 3 in the article by Callaghan outlines general staging criteria for lymphomas.

TREATMENT PRINCIPLES

The treatment of NHL varies widely by histology, or cell type causing the disease, and stage, or amount and location of tumors in the body. The approach to a low-grade lymphoma will be quite different from that of a high-grade tumor, as each will behave quite distinctly, with almost an opposite natural history.

Low-grade tumors (WF subsets A to C) tend to progress slowly, and are often asymptomatic for long periods. With or without treatment, the natural course of the disease may fluctuate considerably over 5 to 10 or more years. However, as benign as this course may appear, low-grade lymphoma cells eventually transform into a more aggressive leukemia/lymphoma-like process and cause the death of the patient soon after. As a result, this chronic, indolent disease is usually felt to be incurable, and many controversies exist related to treatment standards, especially in those patients who present with disseminated disease.

The progression of intermediate- and high-grade lymphomas (WF subsets D to J) is similar to that of other cancers. They are diagnosed in the presence of symptomatology, grow and metastasize more consistently, and cause death if left untreated. However, due to their higher growth fraction, these tumors tend to be more chemosensitive and radiosensitive, and therefore demonstrate higher response rates when treated.

Typically, combination chemotherapy is offered to produce shrinkage of disease and, hopefully, complete regression. Combinations are chosen from active agents with differing mechanisms of action to provide maximal cell kill even during short infusions. Cyclophosphamide and doxorubicin are very active against lymphoma, as is methotrexate to a slightly lesser extent. These agents usually are used in today's protocols in various schedules and doses. Table 3 outlines common regimens used for both primary treatment and salvage in the NHL population.

A relationship seems to exist between the growth fraction of the tumor cells and their response to increasing dose intensity, which is defined as the dose of drug per unit of time. In animal models, a nonlinear relationship has been demonstrated wherein doubling the drug dose in a single time period may increase cell kill 10-fold, and a dose reduction of as little as 20% may decrease the cure rate by 50%.[29] In humans, a study by Kwak et al[30] examined the relative dose intensity of each drug in the CHOP, M-BACOD, and MACOP-B regimens when administered to 115 previously untreated intermediate-grade NHL patients. These investigators found a correlation between dose intensity and survival, and when a multivariable analysis of prognostic factors was performed, the most important predictor of survival was a relative dose intensity of doxorubicin greater than 75%, where 100% equals the full dose of the drug in the CHOP regimen.[30]

TABLE 3. Common NHL Chemotherapy Regimens

Primary treatment	
CHOP	Cyclophosphamide/hydroxyldaunorubicin or doxorubicin/vincristine/prednisone
m-BACOD	Methotrexate/bleomycin/doxorubicin/cyclophosphamide/vincristine/ dexamethasone
ProMACE-CytaBOM	Prednisone/methotrexate/doxorubicin/cytarabine/bleomycin/vincristine/ methotrexate
MACOP-B	Methotrexate with leucovorin rescue/doxorubicin/cyclophosphamide/vincristine/prednisone/ bleomycin
ProMACE-MOPP	Prednisone/methotrexate/doxorubicin/cytarabine/ mechlorethamine/vincristine/procarbazine/ prednisone
CVP	Cyclophosphamide/etoposide/ cisplatin
COPA	Cyclophosphamide/vincristine/ doxorubicin/prednisone
CHVP	Cyclophosphamide/doxorubicin/ teniposide/prednisone
Salvage treatment	
IMVP-16	Ifosfamide/methotrexate/etoposide
MIME	Methyl-gag/ifosfamide/methotrexate/etoposide
ESHAP	Etoposide/cytosine arabinoside/ cisplatin/methylprednisolone
Transplantation	
BEAC	BCNU/etoposide/cytosine arabinoside/cyclophosphamide
BEAM	BCNU/etoposide/cytosine arabinoside/melphalan
DHAP	Dexamethasone/high-dose cytarabine/cisplatin

Controversy regarding a first-line standard of care regimen still remains. A recent study sought to compare four commonly used regimens, including CHOP, ProMace-CytaBOM, m-BACOD, and MACOP-B. Eight hundred ninety-nine patients with intermediate- and high-grade NHL were randomized between the four regimens and were followed for short-term response (partial or complete [CR] remissions) as well as for long-term response (disease-free and overall survival) at 3 years posttreatment. In the short term, it appeared that CHOP was slightly less effective in inducing partial remission and CR. After 3 years of

follow-up, however, there were no significant differences in disease-free and overall survival, and the incidence of treatment-related mortality in the CHOP group was significantly lower. These findings affirm the practice of using CHOP as first-line therapy in many academic and community settings.[31]

Treatment of Low-Grade Non-Hodgkin's Lymphoma

For patients with low-grade NHL in stage I-II, radiation therapy alone may be curative, although reports of recurrence beyond 10 years are seen. These lymphomas tend to recur in sites distant from the original field of therapy, such as extranodally, or in other lymph node regions.[32] Depending on whether the site of disease is supradiaphragmatic or subdiaphragmatic, typical fields used as single-modality therapy include mantle and inverted "Y" field irradiation. Total lymphoid irradiation is unlikely to be advocated as a primary intervention in early low-grade lymphoma as its benefit has not been demonstrated clinically and its use has the potential to render a patient ineligible for transplantation later in their disease course due to bone marrow or other organ damage.

Management of stage III and IV low-grade lymphoma with any modality remains controversial. In asymptomatic patients, a "watch and wait" approach may be offered, as a classic study by Rosenberg and Kaplan[33] showed that there was no survival advantage for patients treated at the time of initial diagnosis. Despite a lower CR rate than combination chemotherapy might offer, single-agent chemotherapy continues to be used routinely at several centers. It may be offered as an alternative for those patients with minor symptoms or for those who are unwilling to take an expectant approach without some form of treatment.[34] This can be a successful long-term tactic, as Rosenberg and Kaplan[33] also showed that if single-agent therapy is delivered for more than 1 year, overall survival is similar compared with combination therapy, such as CVP.[33]

Combinations such as CHOP, with or without radiotherapy, are another possible modality for disseminated (stage III-IV) low-grade disease. Concurrent radiotherapy and chemotherapy, especially when using total lymphoid irradiation, may limit the intensity of the chemotherapy able to be provided due to toxicity.[35]

A National Cancer Institute prospective randomized study comparing aggressive initial therapy versus watchful waiting helps to further illustrate the frustration found in treating this patient population. Eighty-nine patients were offered either ProMACE/MOPP followed by low-dose total lymphoid irradiation or observation. Disease-free survival after 4 years of follow-up was striking at 51% in the treatment group versus 12% in the observed patients. However, at the study's conclusion, no difference in overall survival was observed.[36] This is typical of the current data comparing initial aggressive therapy versus observation or less aggressive therapy in stage III-IV low-grade NHL patients, and contributes to the confusion related to a standard of care for this group.

Treatment of Intermediate-Grade Non-Hodgkin's Lymphoma

Before the evolution of effective combination chemotherapy regimens, radiotherapy alone was the primary intervention for patients with localized (stage I-II) intermediate-grade NHL. A clear advantage has since been demonstrated by incorporating cytotoxic agents into treatment protocols, and in fact they have probably supplanted radiotherapy in this patient population. Targeted use of radiotherapy to decrease tumor bulk is clinically beneficial and still remains common.

Stage III-IV intermediate-grade lymphoma patients require combination chemotherapy as an immediate intervention, and those patients presenting with high-risk disease according to the International NHL Prognostic Factors Index should be especially offered aggressive regimens that provide higher dose intensities.[23] High-risk factors are age over 60 years, stage III-IV disease, elevated lactate dehydrogenase, and poor performance status.

Treatment of High-Grade Non-Hodgkin's Lymphoma

The diagnosis of a high-grade NHL (WF subtypes H to J) prompts immediate and aggressive action. Depending on cellular histology, these patients present with rapidly growing disease, which has the potential to double in bulk within days or hours. Treatment mandates dose-intense chemotherapy, with or without radiotherapy, and prophylactic central nervous system therapy. It is necessary to prophylax the central nervous system as the blood-brain barrier prevents the perfusion of systemic chemotherapy into this compartment,

and prevents destruction of micrometastases seeking a sanctuary site. These patients are also excellent candidates for transplantation (to be discussed in more detail later) as the high growth fraction of the tumors responds dramatically to the super-dose intensity of transplant preparative regimens.

Salvage

Unfortunately, 30% to 60% of patients will not achieve CR or will ultimately relapse after receiving standard-dose chemotherapy regimens, and will require "salvage" therapy to offer control.[37] Conventional salvage regimens include IMVP-16, MIME, and DHAP. Although none of these offers patients more than a small likelihood of surviving 2 years after treatment,[38-40] ESHAP, another salvage regimen, is intended for aggressive control of disease, not palliation. It has been found to be most effective in chemosensitive patients who had no evidence of bulky disease or B symptoms. A controversy exists related to the effectiveness of this regimen after initial reports of a *65%* response rate at M.D. Anderson Cancer Center (Houston, TX)[41] were not able to replicated by a UK study, which had no responders.[42] A later study by King Faisal Specialist Hospital and Research Centre (Riyadh, Saudi Arabia) confirmed the efficacy of ESHAP when used aggressively in patients who have previously achieved a CR.[43] The UK study included older patients who were initially resistant to therapy, thereby reinforcing the need to apply therapy to appropriate patients in appropriate situations, and to be clear on the intent of therapy when formulating the treatment plan. *An* attempt to "secretly" palliate, perhaps at the patient or family's request, by using an aggressive salvage regimen in diluted doses actually may be less effective than using a known palliative regimen.

Biological Response Modifiers

The prospect of using the body's own innate immune system to act on a malignancy has recently become reproducibly successful in clinical practice. The increasing interest in biological response modifiers to treat malignancies such as NHL may test in part on the inability of standard chemotherapy to sustain a durable remission. Biological response modifiers are used in several ways to treat lymphoma. Proteins such as hematopoietic growth factors support the patient through the deleterious effects of other treatment modalities while interferons (IFNs), interleukins, and monoclonal antibodies spur the body's own immune system to act directly against the tumor cells. Each biotherapeutic agent plays an important part in successful therapy.

Interferons. The antiproliferative effects of IFNs have been known since the 1960s, but it was the availability of human interferons in the 1970s that spurred research into their use in a host of malignancies.[44] Interferons can induce intracellular protein activity by enhancing the immune surveillance properties of natural killer cells and changing the cell surface of the tumor cells.[45]

Interferons are used as monotherapy to induce regression or remission in patients with follicular lymphoma, low-grade T-cell lymphoma, and hairy cell leukemia/lymphoma. They have not shown as great a response as single agents in intermediate- or high-grade disease.[44] In one of the first studies using IFN-α-2a for the treatment of NHL, Foon et al[46] reported responses in 13 of 24 low-grade patients, with only two of six intermediate and one of seven high-grade patients responding. Overall, the response rate for those with follicular lymphomas is most impressive, with approximately a 50% response rate in one series.[44]

Animal models have suggested that IFN-a-2a and chemotherapy agents with activity against low-grade lymphoma may act synergistically, spurring investigations into combining these modalities. Because of *the* slow induction of remission by IFN-α-2a alone, it is logical to incorporate an effective chemotherapy regimen to promote the best response, then use IFN-α-2a to prolong remission. It also has been questioned whether, despite the known additive myelosuppression of concomitant IFN and chemotherapy, they should be combined from the start due to the prolonged time to maximal effect of the IFN therapy. Several studies have sought to illustrate this hypothesis, including Smalley et al's work[47] in an Eastern Cooperative Oncology Group study in which COPA alone or COPA plus IFN-α-2a was given to previously untreated patients. Response rates were not significantly different, but an 11-month event-free survival benefit and an increase in the 3-year survival rate from *68%* to 76% ($P = .014$) were gained. Unfortunately, a 5-year update of these data showed no overall survival benefit at that time.[47]

The Group d'Etudes des Lymphomes des l'Adulte conducted a similarly intended study with 242 previously untreated patients, randomizing them

to either CHVP alone for 18 months versus CHVP plus IFN-a-2b for the same period. The patients who received IFN along with CHVP had significantly higher response rates, as well as event-free and overall survival rates at 3 years.[48]

Side effects of IFN therapy, while quite unlike the effects typically associated with traditional chemotherapy regimens, can be dose-limiting. A flu-like syndrome is common among all multilineage cytokines. Due to activation of the cytokine cascade, it includes fever, fatigue, headache, chills, and myalgia. These symptoms may be dose and route dependent, and as the onset of the syndrome usually can be anticipated approximately 2 to 3 hours after administration, acetominophen may be used prophylactically to lessen the severity. Some patients find administration before bedtime to be helpful in managing the experience and, in many patients the appearance of symptoms also lessens with subsequent doses. In a subset of patients, these symptoms may become the dose-limiting toxicity. Careful nursing support and persistent symptom management may be the difference between successful completion and discontinuation of therapy, even in a patient who is responding to IFN therapy.

When used concomitantly with chemotherapeutic agents, IFN may limit further therapy by leading to myelosuppression throughout the platelet, red blood cell, and neutrophil cell lines. Central nervous system toxicity, especially depression, may occur, but as IFN does not cross the blood-brain barrier, this effect is thought to be due to other cytokines released in response to IFN administration.[44]

Monoclonal antibodies. In November 1997, rituximab, a monoclonal antibody specifically targeted to the CD20 B cell, was approved by the Food and Drug Administration to treat patients with relapsed or refractory follicular, CD20-positive, B-cell NHL. Rituximab is unconjugated, meaning that it is not bound to another molecule, such as other diagnostic monoclonal antibodies have been. The primary mechanism of action for this molecule consists of fixing complement to the target CD20 receptor, thereby activating the specific immune system (also known as complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity). Cytotoxic T lymphocytes and natural killer cells may then recognize the malignant B cell as tumor and destroy it throughout the body. Another possible mechanism of action relates to a proposed function of the CD20 receptor as a cell cycle regulator. By binding rituximab to this receptor site, the antibody may affect propagation of the tumor cells.[49]

Transplantation

The first successful report of treating lymphoma with autologous bone marrow transplantation was in 1978 by Appelbaum et al.[50] Since that time, the use of cellular supportive techniques such as bone marrow and peripheral stem cell transplantation (collectively referred to here as transplantation) have become widespread, and in many cases, no longer the exclusive domain of clinical research. Transplantation in patients with NHL has become increasingly common in community settings, with the decreased morbidity related to the technique and ability to deliver greater proportions of the therapy on an outpatient basis, thereby rendering it easier to provide outside academic settings.

Originally used when even salvage regimens failed, other indications for this type of therapy are being studied. A movement from treatment of last resort to use as a targeted early intervention is under way, and this appeals theoretically in diseases such as lymphoma in which dose intensity is a known key driver of successful therapy.

As previously discussed, the behavior and treatment of low-grade NHL differs greatly from intermediate- and high-grade lymphoma. Hesitancy arose regarding the appropriateness of using such an intense regimen in patients whose natural course of disease may leave them asymptomatic for another decade. The lack of progress in preventing the transformation of these cells into a more aggressive tumor type, or in treating them once transformed, has recently shifted consensus toward moving transplantation research forward in low-grade patients.

Several studies in low-grade NHL report CR rates that range from 40% to 75%,[51-54] but follow-up time has been relatively short, and due to the prolonged natural history of this tumor type, further evaluation is needed to assess durability. Most of the mature data have come from studies in which patients with low-grade NHL who are in their second or more relapse or those refractory to standard chemotherapy are treated with high doses of cyclophosphamide and total body irradiation. An advantage in freedom from progression is typically shown, but thus far no survival advantage is evident, possibly due to mortality related to the procedure or to an increase in myelodysplastic

syndrome years after the high-dose therapy has been given.[54]

In the arena of intermediate- and high-grade NHL, an important intergroup study evaluating the efficacy of conventional salvage treatment versus transplant showed the advantage of increased dose intensity in these tumor types. One hundred twenty-five patients who relapsed after a previous CR were randomized to receive either four courses of DHAP and radiotherapy, or the preparative regimen BEAC with or without radiotherapy, followed by autologous bone marrow transplantation (ABMT). Response rate in the DHAP group was 44%, compared with **84%** after ABMT. After ***63*** months of follow-up, event-free survival in the DHAP group was **12%** versus **46%** in the ABMT group ($P = .001$). The 5-year overall survival rate was also significantly improved in the ABMT patients, at **53%** versus **32%** in the DHAP group ($P = .038$).[55]

The leading data comparing ABMT with peripheral blood progenitor cell therapy (PBPC or stem cell transplant) came from a study by Schmitz et al,[56] in which 58 patients with Hodgkin's disease or high-grade NHL received BEAM preparation followed by either granulocyte colony-stimulating factor–mobilized PBPC infusion or ABMT. In the granulocyte colony-stimulating factor–mobilized PBPC group, patients experienced significant reductions in time to platelet and neutrophil recovery and required significantly fewer transfusions of packed red blood cells and platelets than the **ABMT** group.[56] In stem cell mobilization, the only significant side effect associated with granulocyte colony-stimulating factor administration is medullary bone pain, which is generally well-controlled with nonnarcotic analgesics. These findings, coupled with the significantly shorter hospitalizations needed in the PBPC group, explain the increasing utilization of granulocyte colony-stimulating factor–mobilized stem cell product during transplantation.

An interesting and promising area of research demonstrated by several centers is that of marrow manipulation. Altering the natural contents of the harvested product so that malignant clonal cells are removed or neutralized may be a major step toward improving this type of therapy. Controversy still exists regarding the effect that reinfusing tumor cells present in marrow product may have on disease recurrence, but the recurrence rate of Patients who received manipulated marrow was significantly better than those patients who received a "contaminated" infusion.[57]

Also intriguing is the potential for the use of biotherapy to augment the immune system after the patient has recovered from the transplantation. In the minimal residual disease state presumed after high-dose chemotherapy, activation of the immune surveillance system to recognize and eradicate remaining or recurring microscopic tumor cells is feasible, and may actually become a standard part of multimodal therapy.

NURSING IMPLICATIONS

The heterogeneous nature of NHL challenges the oncology nurse to meet a variety of physical and psychosocial needs for both patients and families. An understanding of the varied presentations and treatment options provides the basis for nursing interventions and education.

Lewis[58] observed that while the medical process from diagnosis to cure, or diagnosis to recurrence and death, identifies critical points along the disease trajectory for health care providers, it is not the same trajectory experienced by the patient and family. The family must somehow also manage the demands of the diagnosis, treatment, and impact of the disease on daily routines and patterns. Health care professionals often assume that patients with supportive families will manage well on their own, but growing evidence suggests that family members share the strain of the illness and require support.[59]

Nurses have a unique opportunity to be advocates for patients with NHL and their families. It is critical that nursing objectives change along with the treatments and goals of therapy.

CONCLUSION

It is recognized that NHL is not just one disease, but actually a host of diseases that arise from the lymphoid system in the bone marrow and take up residence in other sites, both in and out of the lymph nodes. Careful evaluation of risk factors and physical signs and symptoms may lead to a diagnosis with one of a variety of diseases, each with its own behavior and treatment principles. Whether watchful waiting is prescribed in the low-grade patient, or granulocyte colony-stimulat-

ing factor–mobilized PBPC therapy in the person with high-grade NHL, the nurse's guiding responsibilities remain essentially the same. We must guard with equal vigilance against both untoward physical effects and psychosocial distress, and use the nursing process to maintain the patient's greatest possible degree of wellness wherever the disease continuum may lead.

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