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THERAPY

EXPERIMENTAL AND CLINICAL PHARMACOLOGY

CLINICAL MEDICINE

MORPHOLOGY

THERAPY

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THE STAGE AT DIAGNOSIS CAN HELP DOCTORS CHOOSE APPROPRIATE TREATMENTS AND PREDICT HOW SOMEONE WITH LYMPHOMA WILL DO IN THE LONG TERM

Non-Hodgkin lymphomas (NHL) are a heterogeneous group of disorders involving malignant monoclonal proliferation of lymphoid cells in lymphoreticular sites, including lymph nodes, bone barrow, the spleen, the liver, and the GI tract. Presenting symptoms usually include peripheral lymphadenopathy. However, some patients present without lymphadenopathy but with abnormal lymphocytes in circulation. Compared with Hodgkin lymphoma, there is a greater likelihood of disseminated disease at the time of diagnosis.

Most NHL are of B-cell origin.

B-NHL – are a heterogeneous group of malignancies that, with the exception of mantle cell lymphoma, arise by malignant transformation of B cells within the germinal center, (GC).

NHL is the most prevalent hematopoietic neoplasm, presenting approximately 4% of all cancer diagnoses and ranking seventh in frequency among all cancers. NHL is more than 5 times as common as Hodgkin disease.

Incidence varies with race; white people have a higher risk than black and Asian American people. In general, the incidence of NHL is slightly higher in men than in women, with a male-to-female ratio of approximately 1,4:1. The ratio may vary depending on the subtype of NHL, however; for example, primary mediastinal diffuse large B-cell lymphoma occurs more frequently in females than in males.

The median age at presentation for most subtypes of NHL is older than 50 years. The exceptions are high-grade lymphoblastic and small noncleaved lymphomas, which are the most common types of NHL observed in children and young adults. At diagnosis, low-grade lymphomas account for 37% of NHLs in patients aged 35-64 years but account for only 16% cases in patients younger than 35 years. Low-grade lymphomas are extremely rare in children.

The cause of NHL is unknown, although, as with the leukemias, substantial evidence suggests a viral cause (e.g. human T-cells leukemia- lymphoma virus, Epstein-Barr virus, hepatitis C virus, HIV). Risk factors for NHL include immunodeficiency (secondary to posttransplant immunosuppression, AIDS, primary immune disorders, sicca syndrome, RA), *Helicobacter pylori* infection, certain chemical exposures, and previous treatment for Hodgkin lymphoma. NHL is the 2nd most common cancer in

HIV-infected patients and some AIDS patients present with lymphoma. *C-myc* rearrangements are characteristic of some AIDS-associated lymphomas.

The exact cause of non-Hodgkin lymphoma is unclear, but doctors have identified some risk factors, such as:

- having conditions that weaken the immune system, like AIDS (acquired immunodeficiency syndrome).
- taking immune-suppressing medications after organ transplants
- exposure to certain viruses, such as Epstein-Barr virus (the virus that usually causes mono)
- having a sibling with the disease.

HCV infection may be a likely cause of various B cell dysregulation disorders such as non-Hodgkin lymphoma and cryoglobulinemia. Based on current findings, it has been hypothesized that NHL and cryoglobulinemia in HCV infection may have an immune-mediated pathogenesis. In HCV infected patients, we showed an elevated risk of these two diseases.

Most (80 to 85%) NHLs arise from B cells; the remainders arise from T cells or natural killer cells. Either precursor or mature cells may be involved. Overlap exists between leukemia and NHL because both involve proliferation of lymphocytes or their precursor. A leukemia-like picture with peripheral lymphocytosis and bone marrow involvement may be present in up to 50% children and in about 20% of adults with some types of NHL. Differentiation can be difficult, but generally patients with more extensive nodal involvement (especially mediastinal), fewer circulating abnormal cells, and fewer blast forms in the marrow (<25%) are considered to have lymphoma. A prominent leukemic phase is less common in aggressive lymphomas, except Burkitt's and lymphoblastic lymphomas.

A retrospective analysis of 140 patients with non-Hodgkin's lymphoma in clinical stage I or II classified according to a modified Lukes and Collins scheme was performed. Three major groups were found according to cell type, with different clinical features:

1. Small cell lymphomas with a relatively favorable survival in spite of high relapse rates.
2. Large cell lymphomas with lower relapse rates, but short time between relapse and death, and unfavorable survival.
3. Mixed small/large cleaved follicular centre cell lymphoma which was most favorable with respect to relapse and survival.

Nodular lymphoma had the same overall relapse rate as diffuse lymphoma, but had a significantly longer survival. Tumors stage I were associated with significantly longer relapse-free survival and survival than stage II. The importance of separating the majority of non-Hodgkin's lymphomas into three main groups according to cell type is emphasized. These major groups require clinical approaches in terms of staging and treatment.

Pathologic classification of NHLs continues to evolve, reflecting new insights into the cells of origin and the biologic bases of these heterogeneous diseases. The

WHO classification is valuable because it incorporates immunophenotype, genotype, and cytogenetics, but numerous other systems exist (e.g. Lyon classification). Among the most important new lymphomas recognized by the WHO system are mucosa-associated lymphoid tumors; mantle cell lymphoma (previously diffuse small cleaved cell lymphoma); and aplastic large cell lymphoma, a heterogeneous disorder with 75% of cases of T-cell origin, 15% of B-cell origin, and 10% unclassified. However, despite the plethora of entities, treatment is often similar except in certain T-cell lymphomas.

The WHO Classification (Table 1) divides NHL into INDOLENT and AGGRESSIVE groups based on morphology, tumor grade, and other prognostic factors.

Table 1.

Subtypes of Non-Hodgkin lymphomas (WHO Classification)

Cell Origin	Tumor
Precursor B-cell tumor	Precursor B-lymphoblastic leukemia/lymphoma*
Mature B-cell tumors	B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma* B-cell prolymphocytic leukemia† Lymphoplasmacytic lymphoma† Splenic marginal zone B-cell lymphoma (±villouis lymphocytes)† Hairy cell leukemia† Plasma cell myeloma/plasmacytoma† Extranodal marginal zone B-cell lymphoma (± monocytoid B cells)† Follicular lymphoma† Mantle cell lymphoma‡ Diffuse large B-cell lymphomas* (including mediastinal large B-cell lymphoma and primary effusion lymphoma) Burkitt's lymphoma*
Precursor T-cell tumor	Precursor T-lymphoblastic leukemia/lymphoma*
Mature B-cell tumors	T-cell prolymphocytic leukemia† T-cell granular lymphocytic leukemia* Aggressive NK cell leukemia* Adult T-cell lymphoma/ leukemia* (HTLV 1-positive) Extranodal NK/T-cell lymphoma, nasal type* Enteropathy-type T-cell lymphoma* Hepatosplenic γ-δ T-cell lymphoma* Subcutaneous panniculitis-like T-cell lymphoma* Mycosis fungoides/Sezary syndrom† Anaplastic large cell lymphoma, T/null cell, primary cutaneous type* Anaplastic large cell lymphoma, T/null cell, primary systemic type* Peripheral T-cell lymphoma, not otherwise characterized* Angioimmunoblastic T-cell lymphoma*

*Aggressive.

†Indolent.

‡Indolent but more rapidly progressive.

HTLV=human T-cell leukemia virus 1; MALT=mucosa-associated lymphoid tissue; NK=natural killer; ±=with or without

Lymphomas are commonly also categorize as indolent or aggressive. Indolent lymphomas are slowly progressive and responsive to therapy but are not curable with standard approaches. Aggressive lymphomas are rapidly progressive but responsive to therapy and often curable.

In children, NHL is almost always aggressive. Follicular and other indolent lymphomas are very rare. The treatment of these aggressive lymphomas (Burkitt's, diffuse large B-cell, and lymphoplasmacytic lymphoma) presents special concerns, including GI tract involvement (particularly in the terminal ileum); meningeal spread (requiring CSF prophylaxis or treatment); and other sanctuary sites of involvement (e.g., testes, brain). In addition, with these potentially curable lymphomas, treatment adverse effects as well as outcome must be considered, including late risks of secondary cancer, cardiorespiratory sequelae, fertility preservation, and developmental consequences. Current research is focused on these areas as well as on the molecular events and predictors of lymphoma in children.

The clinical manifestations of non-Hodgkin lymphoma (NHL) vary with such factors as the location of the lymphomatous process, the rate of tumor growth, and the function of the organ being compromised or displaced by the malignant process.

The Working Formulation classification groups the subtypes of NHL by clinical behavior – that is, low-grade, intermediate-grade, and high-grade. Because of Working Formulation is limited to classification based upon morphology, it cannot encompass the complex spectrum of NHL disease, excluding important subtypes such as mantle cell lymphoma or T cell/natural killer cell lymphomas. However, it continues to severe as a basic for understanding the clinical behavior of groups of NHLs.

Peripheral adenopathy that is painless and slowly progressive is most common clinical presentation in these patients. Spontaneous regression of enlarged lymph nodes can occur in low-grade lymphoma, potentially causing confusion with an infectious condition.

Primary extranodal involvement and B symptoms (i.e., temperature >38 °C, night sweats, weight loss >10 % from baseline within 6 months) are not common at presentation, but they are common in patients with advanced, malignant transformation (i.e., evolution from a low-grade to an intermediate- or high-grade lymphoma) or end-stage disease.

Bone marrow is frequently involved and may be associated with cytopenia or cytopenias. Fatigue and weakness are more common in patients with advanced-stage disease.

These types of lymphomas cause a more varied clinical presentation. Most patients present with adenopathy. More than one third of patients present with extranodal involvement; the most common sites are the gastrointestinal (GI) tract (including the Waldeyer ring), skin, bone marrow, sinuses, genitourinary (GU) tract, thyroid, and central nervous system (CNS). «B-symptoms» are more common, occurring in approximately 30-40 % of patients.

Lymphoblastic lymphoma, a high-grade lymphoma, often manifests with an anterior superior mediastinal mass, superior vena cava (SVC) syndrome, and leptomeningeal disease with cranial nerve palsies.

Patients with Burkitt lymphoma (occurring in the United States) often present with a large abdominal mass and symptoms of bowel obstruction. Obstructive hydronephrosis secondary to bulky retroperitoneal lymphadenopathy obstructing the ureters can also be observed in these patients.

Primary CNS lymphomas are high-grade neoplasms of B-cell origin. Most lymphomas originating in the CNS are large cell lymphomas or immunoblastomas, and they account for 1 % of all intracranial neoplasms. These lymphomas are more commonly observed in patients who are immunodeficient because of conditions such as Wiskott-Aldrich syndrome, transplantation, or AIDS.

Low-grade lymphomas may produce peripheral adenopathy, splenomegaly, and hepatomegaly. Splenomegaly is observed in approximately 40 % of patients; the spleen is rarely the only involved site at presentation.

Intermediate- and high-grade lymphomas may produce the following physical examination findings:

• Rapidly growing and bulky lymphadenopathy
• Splenomegaly
• Hepatomegaly
• Large abdominal mass: this usually occurs in Burkitt lymphoma
• Testicular mass
• Skin lesions: lesions are associated with cutaneous T-cell lymphoma(mycosis fungoides), anaplastic large-cell lymphoma, andangioimmunoblastic lymphoma

Potential disease-related complications include the following:

• Cytopenias (i.e., neutropenia, anemia, thrombocytopenia) secondary to bone marrow infiltration; alternatively, autoimmune hemolytic anemia is observed in some types of NHL (e.g., small lymphocytic lymphoma /chronic lymphocytic leukemia (SLL/CLL))
• Bleeding secondary to thrombocytopenia, disseminated intravascular coagulation (DIC), or vascular invasion by the tumor
• Infection secondary to leukopenia, especially neutropenia
• Cardiac problems secondary to large pericardial effusion or arrhythmias secondary to cardiac metastases
• Respiratory problems secondary to pleural effusion and/or parenchymal lesions
• Superior vena cava (SVC) syndrome secondary to a large mediastinal tumor
• Spinal cord compression secondary to vertebral metastases
• Neurologic problems secondary to primary CNS lymphoma or lymphomatous meningitis
• GI obstruction, perforation, and bleeding in a patient with GI lymphoma (may also be caused by chemotherapy)
• Pain secondary to tumor invasion
• Leukocytosis (lymphocytosis) in leukemic phase of disease

Diagnosis

• Chest X-ray

• CT of chest, abdomen, and pelvis (possibly integrated PET–CT)

• CBC, ESR, alkaline phosphatase, LDH, liver function tests, albumin, Ca, BUN, creatinine, electrolytes, and uric acid

• HIV, hepatitis B virus, and hepatitis C virus testing

• Lymph node and bone marrow biopsy

• MRI of spine if neurologic symptoms are present

As with Hodgkin lymphoma, NHL is usually suspected in patients with painless lymphadenopathy or when mediastinal adenopathy is detected on routine chest X-ray. Painless lymphadenopathy can also result from infectious mononucleosis, toxoplasmosis, cytomegalovirus infection, primary HIV infection, or leukemia. Similar chest X-ray findings can result from lung carcinoma, sarcoidosis, or TB. Less commonly, patients present after a finding of peripheral lymphocytosis on CBC done for nonspecific symptoms. In such cases, the differential diagnosis includes leukemia, Epstein–Barr virus infection, and Duncan's syndrome (X-linked lymphoproliferative syndrome).

Chest X-ray is obtained if not done previously, and a lymph node biopsy is done if lymphadenopathy is confirmed on CT or PET scan. If only mediastinal nodes are enlarged, patients require CT-guided needle biopsy or mediastinoscopy. Usually, tests should include CBC, alkaline phosphatase, renal and liver function tests, LDH, and uric acid. Other tests are done depending on findings (e.g., MRI for symptoms of spinal cord compression or CNS abnormalities).

Histologic criteria on biopsy include destruction of normal lymph node architecture and invasion of the capsule and adjacent fat by characteristic neoplastic cells. Immunophenotyping studies to determine the cell of origin are of great value in identifying specific subtypes and helping define prognosis and management; these studies also can be done on peripheral cells. Demonstration of the leukocyte common antigen CD45 by immunoperoxidase rules out metastatic cancer, which is often in the differential diagnosis of «undifferentiated» cancers. The test for leukocyte common antigen, most surface marker studies, and gene rearrangement (to document B–cell or T-cell clonality) can be done on fixed tissues. Cytogenetics and flow cytometry require fresh tissue.

Staging: Although localized NHL does occur, the disease is typically disseminated when first recognized. Staging procedures include CT of the chest, abdomen, and pelvis; PET; and bone marrow biopsy. The final staging of NHL is similar to that of Hodgkin lymphoma and is based on clinical and pathologic findings.

Differential diagnoses

• Hodgkin disease

• Infectious mononucleosis

• Solid tumor malignancies: metastatic disease to lymph nodes secondary to carcinoma, melanoma, or sarcoma

• Other hematologic malignancies or lymphoproliferative disorders: granulocytic sarcoma, multicentric Castleman disease

• Benign lymph node infiltration or reactive follicular hyperplasia secondary to infection (e.g., tuberculosis; other bacterial, fungal, and, rarely, viral infections), and collagen–vascular diseases

• Hodgkin lymphoma, which requires a different treatment strategy than NHL

Treatment

• Chemotherapy, radiation therapy, or both

• Sometimes anti-CD20 monoclonal antibody

• Sometimes hematopoietic stem cell transplantation

Treatment varies considerably with cell type, which are too numerous to permit detailed discussion. Generalizations can be made regarding localized vs advanced disease and aggressive vs indolent forms. Burkitt's lymphoma and mycosis fungoides are discussed separately.

Localized disease (stages I and II). Patients with indolent lymphomas rarely present with localized disease, but when they do, regional radiation therapy may offer long-term control. However, relapses may occur >10 years after radiation therapy.

About 1/2 of patients with aggressive lymphomas present with localized disease, for which combination chemotherapy, with or without regional radiation, is usually curative. Patients with lymphoblastic lymphomas or Burkitt's lymphoma, even if apparently localized, must receive intensive combination chemotherapy with meningeal prophylaxis. Treatment may require maintenance chemotherapy (lymphoblastic), but cure is expected.

Advanced disease (stages III and IV). For indolent lymphomas, treatment varies considerably. A watch-and-wait approach, treatment with a single alkylating drug, or 2- or 3-drug regimens may be used. Criteria considered in selecting management options include age, general health, distribution of disease, tumor bulk, histology, and anticipated benefits of therapy. The B-cell specific anti-CD20 antibody rituximab and other biologic response modifiers appear to be of benefit; one of these drugs can be combined with chemotherapy or administered as single therapy. Radiolabeled-antibody therapy is also valuable.

In patients with the aggressive B-cell lymphomas (e.g., diffuse large B-cell), the standard drug combination is rituximab plus cyclophosphamide, hydroxydaunorubicin (doxorubicin), vincristine, prednisone (R-CHOP). Complete disease regression is expected in 270 % of patients, depending on the IPI category. More than 70 % of complete responders are cured, and relapses >2 years after treatment ceases are rare.

As cure rates have improved with the use of R-CHOP, autologous transplantation is reserved for patients with relapsed or refractory aggressive B cell lymphomas, some younger patients with mantle cell lymphoma, and some patients with aggressive T-cell lymphomas.

Lymphoma relapse. The first relapse after initial chemotherapy is almost always treated with autologous stem cell transplantation. Patients usually should be ≤70 years or in equivalent health and have responsive disease, good performance status, a source of uncontaminated stem cells, and an adequate number of CD34+ stem cells (harvested

from peripheral blood or bone marrow). Consolidation myeloablative therapy may include chemotherapy with or without irradiation. Posttreatment immunotherapy (e.g., rituximab, vaccination, IL-2) is being studied.

An allogeneic transplant is the donation of stem cells from a compatible donor (brother, sister, or matched unrelated donor). The stem cells have a 2-fold effect: reconstituting normal blood counts and providing a possible graft-vs-tumor effect.

In aggressive lymphoma, a cure may be expected in 30 to 50 % of eligible patients undergoing myeloablative therapy.

In indolent lymphomas, cure with autologous transplantation remains uncertain, although remission may be superior to that with secondary palliative therapy alone. Reduced intensity allotransplantation appears to offer a potentially curative option in some patients with indolent lymphoma.

The mortality rate of patients undergoing myeloablative transplantation has decreased dramatically to 2 to 5 % for most autologous procedures and to <15 % for most allogeneic procedures.

Complications of treatment. A late sequela of standard and high-dose chemotherapy is the occurrence of 2nd tumors, especially myelodysplasias and acute myelogenous leukemia. Chemotherapy combined with radiation therapy increases this risk, although its incidence is still only about 3%.

Medication Summary. Multiple chemotherapeutic agents are active against non-Hodgkin lymphoma (NHL) and can be used alone or in combination, depending on the histology and stage of the disease and whether the patient can tolerate chemotherapy. In addition, several biological therapies are currently available for these patients, including interferons, rituximab, and radiolabeled antibodies (the newest biological therapy).

Alkylating agents impair cell function by forming covalent bonds with DNA, ribonucleic acid (RNA), and proteins. These agents are not cell cycle phase-specific and are used for hematologic and nonhematologic malignancies.

Anthracycline antibiotics bind to nucleic acids by intercalation with base pairs of the DNA double helix, interfering with the DNA synthesis. They cause inhibition of DNA topoisomerases I and II.

Vinca alkaloids inhibit microtubule assembly, causing metaphase arrest in dividing cells. Vinca alkaloids are also cell cycle phase-specific at the M and S phase.

Glucocorticoids cause lysis of lymphoid cells, which led to their use against acute lymphoblastic leukemia (ALL), multiple myeloma, and NHL. These agents are also used as adjunctive antiemetic agents, to decrease vasogenic edema associated with tumors, and as prophylactic medication to prevent hypersensitivity reactions associated with some chemotherapeutic drugs.

Antimetabolites cause tumor cell death by inhibiting enzymes that are important in DNA synthesis.

Biological response modulators control the response of the patient's immune system to tumor cells, infecting organisms, or both.

Prognosis. Patients with T-cell lymphomas generally have a worse prognosis than do those with B-cell types, although newer intensive treatment regimens may lessen this difference. Prognosis for each NHL variant is related to differences in tumor cell biology.

Survival also varies with other factors. The International Prognostic Index (IPI) is frequently used in aggressive lymphomas. It considers 5 risk factors:

- Age >60
- Poor performance status (can be measured using the Eastern Cooperative Oncology Group tool)
- Elevated LDH
- >1 extranodal site
- Stage III or IV disease

Outcome is worse with an increasing number of risk factors. Survival, as determined by IPI factor, has improved with the addition of rituximab to the standard chemotherapeutic regimen. Patients in the highest risk groups (patients with 4 or 5 risk factors) now have a 50 % 5-years survival. Low-risk patients without any of the risk factors have a very high cure rate. A modified IPI (follicular lymphoma IPI (FLIPI)) is being used in follicular lymphomas and in diffuse large B-cell lymphoma (revised IPI (R-IPI)).

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