



FREQUENTLY ASKED QUESTIONS ABOUT LYMPHOMA

Lymphoma: Non-Hodgkin's Lymphoma (NHL)

Lymphomas are malignant (cancerous) conditions that usually arise in the lymphatic system (lymph nodes, spleen or bone marrow). One quarter of all lymphomas arise outside the lymphatic system (extranodal lymphomas) such as the stomach, skin, oral cavity and pharynx, small intestine, and brain/central nervous system. In the last 30 years, the incidence of non-Hodgkin's lymphoma (NHL) rose by more than 80 percent in the United States, representing one of the largest increases of any cancer. Currently, NHL represents approximately 4 percent of all cancer diagnoses.

1. What is the cause of non-Hodgkin's lymphoma?

The cause of NHL is unknown. Certain **genetic abnormalities** (chromosomal translocations) are characteristic for certain lymphomas, hinting at a genetic defect that contributes to the development of the disease.

Environmental factors may play a role in the development of NHL. Certain workers have a slightly increased risk of developing NHL, including farmers, pesticide applicators, grain (flour) millers, meat workers, wood and forestry workers, chemists, painters, mechanics, machinists, printers, and workers in the petroleum, rubber, plastics, and synthetics industries. Chemicals that have been linked to the development of NHL include a variety of pesticides and herbicides solvents and organic chemicals, wood preservatives, dusts (wood, cotton), and some components in hair dye.

Patients who receive cancer **chemotherapy** and/or **radiation therapy** are also at increased risk of developing NHL.

Several **viruses** have been implicated in the pathogenesis of NHL, including EBV, and the hepatitis C virus.

Patients with inherited and acquired states of **immunosuppression** also are at increased risk for NHL, such as HIV infection, organ or bone marrow transplant recipients, long-term survivors of Hodgkin's disease.

A variety of **collagen vascular** and **autoimmune diseases** (eg, Sjögren's syndrome, rheumatoid vasculitis and systemic lupus erythematosus) also pose an increased risk of developing NHL.

An increased incidence of **gastrointestinal** (GI) lymphomas is seen in patients with celiac (nontropical) sprue and inflammatory bowel disease, particularly Crohn's disease. Gastric mucosa-associated lymphoid tissue (MALT) lymphoma is seen most frequently, but not exclusively, in association with *Helicobacter pylori* infection.

2. What are symptoms of lymphoma and how can it be screened?

No effective methods are available for screening or identifying populations at high risk for the development of NHL. Fever, weight loss, and night sweats, referred to as



systemic B symptoms, as well as fatigue and weakness, are more common in advanced or aggressive NHL but may be present in all stages and histologic subtypes.

Painless, slowly progressive peripheral adenopathy is the most common clinical presentation in patients with low-grade lymphomas. Patients sometimes report a history of waxing and waning adenopathy before seeking medical attention.

3. How is the diagnosis of NHL established?

A definitive diagnosis can be made only by biopsy of pathologic lymph nodes or tumor tissue. A formal review by an expert hematopathologist for additional studies, such as immunophenotyping and genotyping, should be considered.

Initial diagnostic evaluation of patients with lymphoproliferative malignancy should include:

- Careful history (night sweats, weight loss, fever; neurologic, musculoskeletal, or GI symptoms)
- Physical examination
- Biopsy of peripheral lymphadenopathy
- Chest x-ray (mediastinal or hilar adenopathy, pleural effusions, parenchymal lesions)
- CT scan of the chest (mediastinal, hilar, or parenchymal pulmonary disease)
- CT scan of the abdomen and pelvis (enlarged lymph nodes, splenomegaly, filling defects in liver and spleen)
- Bone marrow biopsy
- Gallium scan (optional/selected cases)
- Bone scan (selected cases) if musculoskeletal symptoms are present or alkaline phosphatase is elevated
- Blood tests: complete blood count (CBC), general chemistry panel, b2-microglobulin are recommended. HIV or HTLV-1 serology in patients with certain subtypes of lymphoma.

Certain subtypes of lymphoma are associated with involvement of the CNS. Sampling of the spinal fluid (lumbar puncture) should be considered in these cases.

Despite an improvement in immunologic, cytogenetic, and molecular techniques used by hematopathologists for diagnosing and classifying lymphoma, many problems and areas of confusion remain.



4. What determines the treatment and prognosis of NHL?

The **stage** or extent of the disease (how many lymph node sites involved, organ involvement, bone marrow involvement etc), **histologic subtype** of lymphoma, and **other clinical prognostic factors**, such as age and certain blood tests determine treatment and prognosis of NHL.

5. What are the different histologic subtypes of lymphoma?

Over the years, several classifications of NHL have been developed. This is sometimes confusing, since several different nomenclatures may exist for the same subtype of NHL depending on which classification system is used.

A **Revised European-American** classification of **Lymphoid neoplasms (REAL classification)** has recently been proposed and is gaining increasing acceptance. The list of lymphoid neoplasms recognized by the REAL classification includes 23 different types of neoplasms. The 13 most frequently occurring clinical entities that are recognized by the REAL classification are listed below: for *practical purposes* these subtypes can be categorized into low grade lymphomas, intermediate grade lymphomas, high grade lymphomas and cutaneous lymphomas.

Low grade lymphomas:

- Follicular lymphoma
- Small lymphocytic lymphoma
- Lymphoma of mucosa associated tissue
- Marginal zone (monocytoid) B-cell lymphoma
- Lymphoplasmacytic lymphoma

Intermediate grade lymphomas:

- Diffuse large B-cell lymphoma
- Mantle cell lymphoma
- Peripheral T-cell lymphoma
- Primary mediastinal large B-cell lymphoma

High grade lymphomas:

- Anaplastic large T- and null-cell lymphoma
- Lymphoblastic lymphoma of T- or B-cell lineage
- Burkitt's-like lymphoma



- Burkitt's lymphoma

HIV (AIDS virus) related lymphomas

6. How is the stage of the disease determined?

Involvement of one lymph node station is designated stage I. If two contiguous sites are involved, is it designated as stage II. This applies to disease that is confined to the same side of the diaphragm.

If disease is present on both sides of the diaphragm, the patient is considered stage III. Bone marrow or organ involvement (lung, liver, etc.) denotes stage IV. If the lymphoma arose outside the lymphatic system (extranodal) such as the liver or lungs, the stage is indexed with an "E." For example a lymphoma presenting as a solitary lung nodule would be considered stage IE.

7. What are other prognostic factors that are associated with survival in patients with NHL?

Several clinical pretreatment characteristics have been identified that are associated with improved survival after therapy for NHL. Besides stage, these are clinical features that were independently predictive of survival:

- Age (greater than 60 years vs. less than 60 years)
- LDH (a blood test)
- Performance status (general health the patient is in: absence of weight loss, weakness, impaired mobility)
- Number of areas containing lymphoma outside of the lymph nodes (i.e. lung, bones, etc.) sites (1 vs. more than 1 site)
- Time to complete remission has been identified as an important treatment-related prognostic factor in aggressive NHL. Patients who require more than 5 cycles of standard chemotherapy to achieve remission have a high risk of relapse.
- Lymphomas with certain cytogenetic abnormalities (involving chromosomes 1, 7, and 17) have a worse prognosis than other lymphomas of similar stage and bulk that do not exhibit these changes.

8. What is the treatment and prognosis for low grade lymphomas?

As a group, low-grade lymphomas are characterized by indolent clinical behavior and comparatively prolonged survival (median survival is 6-10 years). Many low-grade lymphomas present in elderly patients, who often have other serious medical illnesses.



Most patients have advanced-stage disease at diagnosis, and only about 10-20 percent have stage I or II disease. There is little potential for cure when the disease presents in more advanced stages, and treatment is usually palliative.

The standard management of low-grade NHL is controversial and ranges from the “watch and wait” approach to the use of combination chemotherapy regimens. A substantial number of patients are asymptomatic at presentation. However, the majority of patients require treatment within a few years because tumor growth produces symptoms, compromises vital organs, creates anxiety, or is cosmetically unacceptable. Whereas a “watch and wait” approach is appropriate for older patients, newer treatment approaches are being tested in younger patients whose longevity is likely to be reduced by their disease.

Stage I and II disease

Most patients that appear to have early stage disease (stage I or II) actually have widespread disease that remains undetectable in the beginning. Radiation therapy for localized disease has therefore yielded significantly lower disease-free survival in these patients.

Involved-field radiation therapy may be the treatment of choice in localized low-grade NHL of the head and neck; it results in a five-year survival rate of more than 50 percent. Some orbital lymphomas also demonstrate high disease-free survival rates with radiation therapy alone. Moderate-dose locoregional radiation therapy resulting in 10-year disease-free survival has been reported in carefully staged patients, suggesting that some of these patients may be cured. Older patients (more than 55-60 years old) are candidates for watchful waiting or locoregional radiotherapy approaches.

The issue of whether added or adjuvant chemotherapy improves the prognosis of patients with early-stage low-grade NHL remains unresolved. It is not unreasonable to offer adjuvant chemotherapy to selected stage II patients with unfavorable prognostic factors, such as systemic symptoms or more than two (or discontinuous) nodal sites.

Stage III and IV disease

Younger patients - The management of younger patients with advanced low-grade lymphoma is probably the most controversial area in the treatment of NHL. Some of these patients will enjoy prolonged survival without initial therapy. Median disease-free survival is almost always between 1.5 and 3 years, and median overall survival ranges from 5 to 7 years. Patients with stage III disease have a better prognosis than patients with stage IV disease. Overall, 75 percent of patients with stage III disease can be expected to survive 5 years.

Chemotherapeutic options in younger patients with low-grade advanced disease include single-agent chemotherapy (chlorambucil [Leukeran] or cyclophosphamide with or without prednisone), CVP (cyclophosphamide, vincristine, and prednisone), or



CHOP. Newer agents, such as fludarabine (Fludara) and cladribine (2-CdA [Leustatin]), have significant antitumor activity.

Patients with poor prognostic factors - Unfavorable prognostic factors include extent of bone marrow involvement (greater than 20 percent), bulky disease (5-7 cm), more than one extranodal site, LDH greater than 1 times the normal values, elevated b2M, and nonambulatory performance status. Patients with these unfavorable clinical features have reduced longevity and are incurable with standard chemotherapy or combined-modality approaches, and should therefore be considered candidates for investigational clinical trials aimed at improving disease-free and overall survival.

Older patients - Because of concomitant medical problems, older patients with asymptomatic, indolent NHL are often observed closely without any initial therapy. The decision to use any of the standard or newer modalities should be individualized, based on the presence of poor prognostic features and the patient's tolerance of planned therapy. Palliative treatment options include chlorambucil or cyclophosphamide with or without prednisone.

9. What is the treatment and prognosis for the mucosa-associated lymphoid tissue (MALT) subtype of low grade NHL?

Like other low-grade lymphomas, mucosa-associated lymphoid tissue (MALT) lymphomas are probably incurable with standard chemotherapy approaches. The treatment approach to MALT lymphomas is similar to that used for other low-grade NHLs.

MALT lymphoma affecting the stomach is associated with previous *H pylori* infection, but a causative role for this organism is unproven. Complete eradication of *H pylori* after treatment with bismuth and/or omeprazole (Prilosec), amoxicillin, and metronidazole frequently leads to disappearance of symptoms and histologic complete remission. In most cases, some evidence of histologic response to treatment of the *H pylori* infection is evident 2-3 months following eradication of the organism. Antibiotics are very effective in treating gastric MALT lymphomas but patients with no or only partial responses need careful investigation to rule out aggressive NHL.

10. What is the treatment and prognosis of intermediate grade lymphoma?

Stage I and II disease

Multi-drug chemotherapy, together with involved-field radiation therapy, has produced disease-free and overall survival rates significantly superior to those achieved with radiation alone. Using chemotherapy (e.g. 3-4 cycles of CHOP) and radiation therapy has yielded five-year, relapse-free survival rates of 78-95 percent for stage I disease and 70-75 percent for stage II disease. It is best to individualize treatment. Patients with nonbulky (less than 10 cm) nodal disease can be treated with 3-4 cycles of CHOP followed by locoregional radiation. Patients with bulky disease (greater than 10 cm),



including large mediastinal masses, probably benefit from 6-8 cycles of CHOP followed by radiation therapy.

Stage III and IV disease

Although CHOP remains the best available standard therapy, it is curative in less than 50 percent of patients, indicating a need for new treatment approaches. The following recommended treatment strategies should be adjusted according to the level of risk, as defined by the prognostic factors:

Age 60 years or younger with low or intermediate risk factors: Younger patients with “good risk factors” (i.e. normal LDH and ambulatory performance status) have five-year survival rates greater than 50 percent. They should be treated with 6-8 cycles of a standard doxorubicin-containing regimen, such as CHOP.

Age 60 years or younger with relatively high or high risk factors: The five-year survival rate in younger patients with “unfavorable risk factors” (high LDH and/or nonambulatory performance status) is less than 50 percent. These patients should be offered participation in clinical trials of dose-intensive treatment strategies aimed at improving the rates and durability of complete responses.

Efforts to augment the dose intensity of treatment include early autologous bone marrow transplantation (BMT).

Age more than 60 years: All patients over the age of 60 years should undergo evaluation of cardiac, pulmonary, and renal function and coexistent illness, which may complicate therapy.

Most older patients with advanced-stage aggressive NHL have five-year survival rates less than 50 percent as a result of decreased initial response, poor tolerance to therapy, and the need for dose reduction because of age.

Compromised cardiac or pulmonary function: Patients with compromised cardiac function require individualized approaches, such as the use of a regimen that does not contain an anthracycline (Adriamycin). Similarly, bleomycin should not be used in patients with compromised pulmonary function.

Mantle Cell Lymphomas

With standard chemotherapy (e.g. CHOP) the survival of patients with mantle cell lymphoma was poor. Recently, investigators developed an intense chemotherapy regimen (hyper-CVAD/AM) which was originally designed for the treatment of acute lymphoblastic leukemia. After four cycles of this regimen, patients 65 years old and younger were consolidated with either an autologous or allogeneic transplant. The overall survival and event-free survival rates at three years were 92 percent.



10. What is the treatment and prognosis of high grade lymphomas?

In general, patients can be divided into good- or poor-risk groups based on the extent of disease, as defined by the presence or absence of bone marrow or CNS involvement, tumor mass 10 cm, and LDH 1.5 times normal.

Lymphoblastic lymphomas

Lymphoblastic lymphomas are indistinguishable from the lymphoblasts of acute lymphoblastic leukemia (ALL). Patients sometimes exhibit clinical features of both leukemia and lymphoma at presentation or during the course of their disease. Mediastinal masses are seen in 50-70 percent of patients at presentation. Because of the propensity for CNS relapse during the course of lymphoblastic lymphomas, CNS prophylaxis with intrathecal chemotherapy and/or irradiation is part of all successful treatment regimens. The complete response rates are 65-80 percent, with long-term survival rates of 45 percent.

Patients with standard risk (stage I-III and normal LDH) do better than patients with high risk (stage IV; high LDH; bone marrow, CNS, or other extranodal site of involvement). Patients with adverse prognostic features are candidates for consolidation with autologous or allogeneic BMT after the completion of induction therapy.

Small noncleaved cell lymphomas (Burkitt's and non-Burkitt's types)

These are the fastest growing and most aggressive of all the lymphomas. These neoplasms can double in size in a matter of days. High-risk features include elevated LDH, bone marrow involvement, and unresectable tumor masses greater than 10 cm.

A brief, high-intensity, cyclophosphamide-based regimen devised at Vanderbilt University achieved durable responses in about 50 percent of high-risk patients.

Selected patients with high-risk features are candidates for autologous or allogeneic BMT during first complete or partial remission.

11. What is the role of bone marrow/stem-cell transplantation in NHL?

Stem-cell transplantation in poor-risk aggressive NHL in first remission -- Even after achieving a complete remission with standard chemotherapy, poor-risk patients have a high risk of the disease coming back (relapse). Studies adding bone marrow transplantation in this group of patients have shown encouraging results.

Often patients with poor-risk NHL in first complete remission are referred to a transplant center after having received their initial therapy elsewhere. It is appropriate to offer such patients high-dose therapy/stem-cell transplantation as consolidation if they initially present with poor-risk features that put them at very high risk of relapse and decreased survival when treated with conventional approaches.



12. How are cutaneous lymphomas treated?

Mycosis fungoides

The most common lymphoma of the skin, mycosis fungoides, is a cutaneous T-cell NHL. Characterized initially by “eczema” and plaque lesions, mycosis fungoides can gradually progress to generalized skin involvement and formation of skin nodules. It can be treated with a variety of topical and systemic therapies, but the potential for cure is low except for very early-stage disease.

Early-stage disease - Treatments directed at the skin, such as total-skin electron-beam radiation, topical chemotherapy with mechlorethamine or carmustine (BCNU [BiCNU]), and psoralen with ultraviolet A activation (PUVA), are usually used as initial therapy for early-stage disease.

Radiation therapy - Cutaneous lymphomas are highly sensitive to radiation. Individual symptomatic lesions are well palliated with small electron-beam or orthovoltage radiotherapy fields at doses of 2,000 cGy over 2 weeks. Curative radiation therapy involves total-skin electron-beam irradiation. The six-field technique of Stanford University can treat the entire skin surface to a dose of 3,600 cGy in 9-10 weeks. This very demanding approach requires the patient to stand for approximately an hour per day, four days per week. Most responses are of short duration.

13. What is the recommended treatment in AIDS-related lymphoma?

Most lymphomas seen in patients who have HIV infection are of high-grade histology and advanced stage at presentation. Unusual sites of presentation, including the rectum, CNS, and multiple soft-tissue masses. Some patients present with primary CNS lymphoma.

Chemotherapy

Many patients are unable to tolerate aggressive chemotherapy regimens. Attenuated-dose regimens are well tolerated, although hematologic toxicity remains a problem in some patients. CNS prophylaxis with intrathecal chemotherapy is necessary to prevent meningeal dissemination. Dose adjusted EPOCH (etoposide, Oncovin, cyclophosphamide, and doxorubicin HCl) is another successful regimen (overall survival rates around 70 percent).

14. What are some of the newer treatment approaches to NHL?

Chemotherapy attacks lymphoma cells but some degree also healthy cells. Research has led to the development of targeted therapies for NHL. These compounds consist of a protein (monoclonal antibody) that recognizes and attaches itself to a specific structure on the surface of lymphoma cells. The protein carries a substance that is toxic to lymphoma cells. The damaging effects of this toxic substance is focussed on the site of its action: the lymphoma cell.



Rituximab

The FDA recently approved this product for use as a single agent in the treatment of relapsed low-grade NHL, and it is also under investigation for use in combination regimens for other lymphomas, including mantle cell, and aggressive NHL. When administered weekly for 4-8 weeks, rituximab produces a 48-57 percent overall response rate in patients with relapsed low-grade lymphoma.

Tositumomab (Bexxar) and **Y2B8** are compounds that carry a radioactive substance to the lymphoma cells. Preliminary results indicate that tositumomab is an effective agent for the treatment of relapsed low-grade and transformed lymphoma.

15. After the successful completion of treatment, what is the risk of relapse and what kind of follow-up tests should be performed?

Relapse - The most important risk to patients with NHL is relapse. Among patients with diffuse aggressive lymphomas, most recurrences are seen within the first 2 years after the completion of therapy, although later relapses may occur. Early detection of recurrent disease is important because these patients may be candidates for potentially curative high-dose therapy and stem-cell transplantation. Patients with advanced low-grade NHL are at a constant risk of relapse, and late recurrence of disease may be seen, sometimes after the patient has been in remission for more than a decade. Physical examination at 2- to 3-month intervals and follow-up CT scans at 4- to 12-month intervals are recommended. Long-term survivors are at increased risk for second cancers, in particular acute myelogenous leukemia, melanoma, Hodgkin's disease, and cancers of the lung, brain, kidney, and bladder. Transplant recipients are also at increased risk of developing acute myeloid leukemia.