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Treatment decisions for patients with non-Hodgkin's lymphoma: taking into account the type of lymphoma and clinical characteristics of the patient



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Introduction

Non-Hodgkin lymphomas (NHL) are among the most common malignancies worldwide. In the last two decades, significant advances have been made in the classification of these entities. At present, the new classification system has separated NHL into entities that have distinct clinical, pathological and molecular characteristics. Furthermore, patient characteristics have been proposed that allow clinicians to identify high-risk patients and to better tailor the treatment based on both patient and tumor characteristics. The following hypothetical case is intended to highlight some of the more relevant information in the management of two of the most common types of NHL.

Case

A 55-year-old non-smoking man comes to your clinic for a second opinion regarding a recent biopsy of a supraclavicular lymph node. The patient was in good health until 4 months ago when he palpated a left supraclavicular node. Over the next 2 months, the node grew in size slightly but he had no other symptoms. He sought attention at his primary care physician's office. His primary care doctor performed an exhaustive history and physical examination noting only an enlarged left supraclavicular node, 2 cm × 2 cm, non-tender and non-mobile. Additionally, a chest roentgenogram was normal, a tuberculin skin test non-reactive and lab tests includ-

ing a hemogram, chemistry panel and HIV antibody test-were normal. A fine needle biopsy was performed which was interpreted by the pathologist as "reactive hyperplasia". The patient is concerned because the node has continued to grow in size.

This clinical scenario presents several important lessons. To begin, one has to consider the differential diagnosis of an isolated lymph node enlargement in an otherwise healthy middle-aged man. Several factors are important in assessing the significance of an enlarged lymph node: the patient's age, the physical characteristics of the node, the location and the clinical setting associated with the lymphadenopathy. The younger the patient, the more likely a node will be benign. Lymphadenopathy in patients younger than 30 years of age are benign in 80% of the cases, whereas in patients greater than 50 years of age, lymphadenopathy is due to benign causes in only 40% of the cases. The physical characteristics of a node are important. Nodes associated with lymphomas tend to be rubbery, firm, matted together and nontender. Nodes involved by metastatic carcinomas are hard and fixed to underlying tissues. In acute infections, nodes tend to be tender, asymmetrical, matted together and the overlying skin is erythematous. The location of the node(s) is important as well. As an example, supraclavicular or scalene lymphadenopathy usually indicates a lymphoid, gastrointestinal or intrathoracic malignancy. Unilateral jugular or mandibular lymph nodes are more likely to be lymphoma or a non-lymphoid head and neck malignancy. Finally, the clinical setting is of paramount importance in the evaluation of lymphadenopathy. A unilateral submandibular node in a patient with tooth pain and fever is more likely reactive whereas the same unilateral cervical node in a smoker raises the suspicion of a malignancy. Table 1 lists some of the more common diseases associated with lymphadenopathy [1].

In our case under discussion, the lack of constitutional or infectious symptoms would go against an infectious etiology. The lack of a smoking history makes a squamous cell carcinoma of the head and neck less likely. The lack of any abnormalities on ancillary testing (which appropriately included tuberculin skin testing and HIV serology) goes against a metastatic tumor or tuberculosis. Other viral infections such as mononucleosis can cause lymphadenopathy but his age makes this possibility unlikely. However, the characteristics of the lymph node (non-tender and non-mobile), its location, the fact that it is asymmetric, in conjunction with the patient's age should make one suspicious that it is malignant.

Since a lymphoproliferative disorder remained in the differential diagnosis after the thorough exam and unrevealing tests, a biopsy of the node is warranted. While the preponderance of enlarged lymph nodes will ultimately be benign (as such it is reasonable to observe them for 6 weeks before performing a biopsy), the fact that this node had grown over a two-month period supported proceeding with a biopsy. While a fine needle aspirate may be useful and sufficient to diagnose certain malignancies such as squamous cell carcinoma, the false negative rate rises significantly when one is dealing with lymphomas. Therefore, in this situation, an excisional biopsy should have been performed. This provides more material to allow a more accurate diagnosis as well as to permit additional studies (i.e., immunohistochemistry, cultures) if the diagnosis should be lymphoma or remain elusive. Furthermore, cytogenetics play an ever-increasing role in the diagnosis and prognosis of non-Hodgkin lymphomas. Thus, you should request that lymph node tissue be frozen for these studies.

Table 1. Selected diseases associated with lymph node enlargement

Infectious causes
Viral: infectious mononucleosis syndromes, human immunodeficiency virus infection, rubella, infectious hepatitis
Bacterial: streptococci, staphylococci, salmonella, cat-scratch disease, brucellosis
Fungal: histoplasmosis, coccidiomycosis
Chlamydial: lymphogranuloma venereum, trachoma
Mycobacterial: tuberculosis, leprosy
Parasitic: microfiliarisis, toxoplasmosis, trypanosomiasis
Spirochetal: syphilis, yaws, endemic syphilis
Immunologic causes
Rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, drug reactions (phenytoin, hydralazine, allopurinol), angioimmunoblastic lymphadenopathy, Sjögren's syndrome
Malignant causes
Hematologic malignancies (lymphomas, leukemias), tumors metastatic to lymph nodes (melanoma, seminoma, lung, breast, kidney, prostate)
Endocrine and metabolic causes
Hyperthyroidism, Gaucher's disease, Niemann-Pick disease
Miscellaneous causes
Castleman's disease, sarcoidosis, amyloidosis, eosinophilic granulomatosis

At your recommendation, the patient undergoes an excisional biopsy of the enlarged lymph node. The pathologist reviews the specimen and confirms a histological diagnosis of a follicular non-Hodgkin lymphoma. The patient returns to your office for the results and further recommendations. His symptoms and physical examination remain unchanged except for a well-healing scar in the left supraclavicular fossa.

As was your suspicion, the biopsy proves to be consistent with a follicular lymphoma, grade I. You ex-

plain to the patient that follicular lymphomas were previously grouped under "low-grade" lymphomas. "Low-grade" lymphomas tend to have a more indolent biological behavior. Their comparatively slow growth frequently translates clinically into long symptom-free periods. Follicular lymphomas are further subdivided into grades (I through III) depending on the relative proportions of small and large cells (Table 2) [2].

At this point, in order to adequately counsel this patient as to his prognosis and possible treatment options, you must order tests aimed at staging the lymphoma, i.e., assessing, as best possible, the extent of the disease. Staging procedures for this type of lymphoma include imaging studies of the chest, abdomen and pelvis, a bone marrow aspirate and biopsy, hemogram, chemistry panel and a lactate dehydrogenase (LDH) level. The tissue samples obtained from either the lymph node biopsy or the bone marrow aspirate should be sent for cytogenetics.

The patient returns after completing his staging work-up. His imaging studies showed no evidence of lymphadenopathy. The bone marrow was negative for lymphomatous involvement. The LDH was normal and the cytogenetics on the lymph node biopsy showed the presence of t(14;18).

The lack of involvement by lymphoma in any other areas places the stage for this patient at a stage I. The staging classification for non-Hodgkin lymphoma follows the same classification that was originally developed for Hodgkin lymphoma (Table 3) [3]. The main benefits of being able to stage patients are that it allows for consistency in analyzing and treating patients with similar characteristics such that it allows treating physicians to determine the best treatment for an individual patient based on known responses. Most patients with follicular lymphomas present with advanced disease. Only 5% to 15% present with localized disease.

The presence of t(14;18) in the lymph node sample confirms the diagnosis of follicular lymphoma. Ninety percent of follicular lymphomas express this translocation and this characteristic can aid in differentiating follicular lymphoma from reactive hyperplasia [4]. Cytogenetic findings that are characteristic for other lymphoma types are listed in Table 4 [5]. These cytogenetic findings are important not only for diagnostic purposes but may have a role in differentiating patients who obtain a "molecular remission" (i.e., absence of any detectable cytogenetic abnormalities). Early data suggests that pa-

Table 3. Ann Arbor staging criteria [3]

Stage	*Criteria*
IA or IB	One area of nodal or extranodal disease
IIA or IIB	Two or more nodal sites of disease or nodal and proximate extranodal sites on the same side of the diaphragm
IIIA or IIIB	Two or more nodal sites of disease or nodal and proximate extranodal sites of disease on both sides of the diaphragm
IVA or IVB	Disseminated extranodal with or without nodal sites of disease

A: No constitutional symptoms; B: Constitutional symptoms: weight loss >10% of baseline, night sweats and/or persistent fever

Table 2. World Health Organization classification of non-Hodgkin's lymphoma [2]

Precursor Cell Disorders	
B-cell	*T-cell*
Lymphoblastic lymphoma	Lymphoblastic lymphoma
Mature or Peripheral Cell Disorders	
B-cell	*T-cell*
Small lymphocytic lymphoma/ Chronic lymphocytic leukemia	Mycosis fungoides
Follicular (grade I thru III)	Peripheral T-cell (unspecified)
Marginal zone	Angioimmunoblastic
Nodal	Angiocentric (nasal-type)
Mucosa-associated lymphoid tissue	Enteropathy-type intestinal
Splenic	Anaplastic large-cell
Mantle cell	Adult T-cell leukemia /lymphoma
Diffuse large B-cell	
Primary mediastinal large B-cell	
Burkitt	

Table 4. Common cytogenetic abnormalities encountered in non-Hodgkin lymphoma [19]

Translocation	*Involved gene(s)*	*Type of lymphoma associated with translocation*
t(11;14)(q13;q32)	bcl-1	Mantle cell lymphoma (70%)
t(14;18)(q32;q21)	bcl-2	Follicular lymphoma (90%)
		Diffuse large cell lymphoma *de novo* (20%) transformed (100%)
t(3;-)(q27;-)	bcl-6	Diffuse large cell lymphoma(40%)
t(8;-)(q24;-)	C-MYC	Burkitt's lymphoma (100%)
t(2;5)(p23;q35)	NPM/ALK	CD30+ anaplastic large cell lymphoma (80%)
t(9;14)(p13;q32)	PAX-5	Lymphoplasmacytoid lymphoma (50%)
t(17;-)(p13;-)	p53	Small lymphocytic lymphoma /B-cell chronic lymphocytic leukemia (10%)
		Diffuse large cell lymphoma, transformed (90%)
		AIDS-Burkitt's lymphoma (60%)
		Burkitt's lymphoma (30%)

tients who obtain a molecular remission may experience improved survival compared with those that still have detectable cytogenetic abnormalities, even if a complete clinical remission is obtained.

You inform the patient that he has stage I follicular lymphoma. He requests specific details about his prognosis and the treatment options available to him.

As mentioned earlier, follicular lymphomas tend to be indolent in their behavior. Exceptions exist, though, and relate to the "grade" of the follicular lymphoma. In effect, patients with grade I and II types have a more benign course whereas grade III follicular lymphomas behave more like "intermediate" lymphomas [6]. The patient's prognosis, in terms of median survival, is relatively good. Untreated grade I follicular lymphomas allow a median survival of 8 to 10 years for all stages combined. However, stage III and IV patients have shorter survivals and are more likely to have symptoms related to progressive and extensive disease.

Patients with stage I or II follicular lymphomas have longer survival and tend to have an asymptomatic period of a more prolonged nature. Published studies have reported on local radiation therapy for patients with early disease. These studies demonstrate that implementing radiation therapy reduces local recurrences. Some suggest that a cure is possible in selected cases although one of the limitations in interpreting these data is that follicular lymphomas tend to have late relapses and, to date, no treatment has achieved a survival plateau, i.e., patients continue to relapse at greater than 8 years after treatment.

Other studies have looked at not treating patients with early stage follicular lymphoma, the so-called "watch and wait" approach. These studies have demonstrated that the overall survival in these patients is unaffected by delaying treatment until progression is documented [7-9].

Therefore, for this patient, you may offer him either a "watch and wait" approach with frequent assessments (every 2 to 4 months) or radiation therapy to the area of involvement. While systemic therapy is obviously a choice, the limited disease burden should dissuade one from pursuing this option at the present time.

The patient opts for local radiation therapy that is delivered by electron beam therapy (total dose of 3000 cGy over a 20-day period). He had a complete response (defined as a total absence of clinical disease). You continue to see him on a regular basis. He remains without evidence of progression for 4 years. At the last visit, he complains of fatigue. His weight is stable and he has not had any night sweats or fevers. You find no abnormalities on physical examination and his laboratory tests and chest radiograph were normal. The patient is concerned that the lymphoma is relapsing and inquires if there is anything else that should be done.

Although the physical examination and laboratory studies are normal, the patient is having constitutional symptoms that are unexplained. It is therefore not unreasonable to proceed with more extensive imaging such as CT scan of the abdomen and pelvis. If this were negative, one would pursue other causes of fatigue but continue to observe from the standpoint of the lymphoma.

A CT scan of the abdomen and pelvis demonstrates retroperitoneal lymphadenopathy with the largest measuring 2 cm × 2 cm. A CT scan of the chest is normal. You inform the patient of these findings and recommend a biopsy. The patient does not comprehend why another biopsy is warranted since you informed him there was a reasonable chance he would have a late relapse.

The lymphadenopathy is clearly significant and the question posted by the patient is a pertinent and important one. There are several reasons why one should obtain a biopsy again despite the likelihood that he may have recurrent disease. Foremost, the possibility of a second malignancy needs to be addressed. Secondly, even though he may have recurrent follicular lymphoma, the grade could have changed (i.e., now is a grade III) which confers a different biological behavior. There is also the concern that the lymphoma may have "transformed" into a different type altogether.

"Transformation" is a phenomenon seen in patients with follicular lymphomas and describes a change in the histopathology of a lymphoma to a different type. In most cases, follicular lymphomas transform into diffuse large B-cell lymphomas that have a more aggressive behavior. Transformation from a low-grade histology to an intermediate- or high-grade histology is estimated to occur in anywhere from 10% to as many as 70% of patients with low-grade lymphomas. Patients with a transformed diffuse large B-cell lymphoma have an abbreviated survival and, in general, require systemic therapy [10].

Thus, this patient should not only have a biopsy performed of a retroperitoneal node but an entire restaging is warranted, including a bone marrow aspirate and biopsy, should recurrent lymphoma be confirmed. Although an excisional biopsy is mandated for the initial diagnosis of lymphoma, a needle biopsy may be considered in patients that are suspected of having a recurrence. It would not be unreasonable to propose a needle biopsy in this gentleman and proceed to a more invasive procedure only if the needle biopsy material was insufficient for an adequate diagnosis.

The biopsy showed a grade II follicular lymphoma. The bone marrow, however, was found to contain lymphoid aggregates that were suspicious for lymphoma. Immunohistochemical staining for immunoglobulin light chains showed a clonal cell population. The patient now presents for the results and recommendations.

The patient has biopsy-proven recurrence and is symptomatic. The presence of symptomatology is one reason why to proceed with therapy as opposed to observation. In the absence of clonal cell populations in the bone marrow, one would stage the patient as a stage IIA. However, the presence of malignant cells in the marrow places the patient as a stage IVA.

As mentioned earlier, patients with follicular lymphoma in early stages (I/II) can be treated with local therapy or observed. However, in patients with more advanced disease, the question becomes harder. Patients may frequently be asymptomatic but may not feel comfortable with not treating immediately. To further complicate matters, in patients with advanced disease, randomized studies comparing immediate therapy *versus* observation with treatment at progression demonstrated improved disease-free survival for those receiving immediate therapy but overall survival was the same. Therefore, patients should be offered treatment to alleviate symptoms, for rapidly progressive adenopathy (including splenomegaly), effusions or cytopenias. Elderly patients or those with comorbid conditions that preclude therapy will more frequently be observed [8,9].

In this patient, you could then make a recommendation to proceed with therapy to alleviate symptoms with the understanding that overall survival may not be affected.

The patient decides to pursue treatment. Which type of treatment would you recommend?

The type of treatment to recommend is somewhat more difficult. There are essentially three options: cytotoxic chemotherapy, immunotherapy with monoclonal antibodies and/or interferon or a combination of both. Chemotherapy for follicular lymphomas can consist of single-agent (i.e., chlorambucil) or combination regimens. While remissions are obtained earlier with combination regimens, overall survival remains the same when compared to single-agent therapy. With regard to combination therapy, anthracycline-containing regimens are generally favored although there is no one regimen that has shown consistent superiority. The introduction of purine analogues such as fludarabine has shown great promise as well [9,11].

Monoclonal antibodies against CD-20 (a protein expressed on B-lymphocytes) showed activity in patients with relapsed disease. Since then, investigators have incorporated anti-CD-20 antibodies in first-line therapy regimens. Preliminary results are encouraging with an improvement of disease-free survival compared with chemotherapy alone. However, it is yet too early to know whether these results will translate into improved overall survival [12].

Interferon has also been used in the treatment of follicular lymphomas, both as initial treatment in conjunction with chemotherapy and as maintenance therapy after chemotherapy in patients that achieve a complete response. Although various chemotherapy regimens were used in these studies as well as various interferon doses, the data suggests some survival benefit from interferon. However, its use has not been widely implemented [13].

The use of high dose chemotherapy with autologous stem cell rescue has also been studied in patients with follicular lymphomas. This therapy has shown higher complete remission rates but the disease-free survival curves have yet to show a definite plateau. However, the data in this area is promising and certainly an option to be considered, particularly for patients with relapsed disease that have responded to another course of chemotherapy ("chemosensitive relapse") [14].

When considering the type of treatment to recommend, the patient characteristics need to be considered as well. In our case under discussion, the patient is young and otherwise healthy with a good performance status. Thus, he should be able to tolerate more intensive therapy. On the other hand, if he were older or with significant comorbid conditions, you would recommend therapy with less toxicity than combination chemotherapy, such as a single agent or a monoclonal antibody.

Ideally, one would give this patient the opportunity to participate in a clinical trial. The multiplicity of treatment options, none of which have recognized superiority over the others, demands further clinical trials to define the best treatment for patients in this situation. The patient declines your offer to participate in a study due to the long distance to the research center.

You recommend combination therapy to this patient as it will induce a remission quicker and relief his symptoms of fatigue. However, the patient declines and opts instead for single agent therapy due to its ease of administration that allows him to continue with his work-related travels.

The patient completes a 6-month course of therapy with chlorambucil and prednisone and obtains a complete remission. At his 3-year follow-up, he is again complaining of fatigue but in addition has night sweats and has had a 15-pound weight loss since his last visit 3 months ago. On examination, you find an enlarged left inguinal lymph node. The remainder of the examination is negative. However, staging studies show diffuse lymphadenopathy

in the retroperitoneum and mediastinum with an elevated LDH. Bone marrow evaluation did not reveal any evidence of lymphoma. An excisional biopsy of the inguinal node was interpreted as having diffuse large B-cell lymphoma with cytogenetics showing persistence of t(14;18). Additionally, an alteration at chromosome 17 was detected. The patient returns for recommendations.

The patient has recurrent lymphoma that has now transformed into a diffuse histology. The t(14;18) abnormality that was detected in his original biopsy persists. In addition, an abnormality of chromosome 17 was found. This chromosomal area encodes for the p53 gene. Nearly 90% of patients with a transformed diffuse large B-cell lymphoma will have a translocation of 17 [5]. He is now a stage IIIB based on the involvement of both sides of the diaphragm and the constitutional symptoms.

Diffuse large B-cell lymphomas are the most common lymphoma diagnosed. It has more aggressive behavior than follicular lymphomas and 40% to 50% of patients present with "B" symptoms. Nearly 50% of patients will present with stage I/II disease. In contrast to follicular lymphomas, diffuse large B-cell lymphomas will result in death within a relatively short period if untreated. Therefore, all patients should be offered treatment.

In patients that are diagnosed with *"de novo"* diffuse large B-cell lymphoma (i.e., non-transformed), combination chemotherapy is standard. For patients with stage I or non-bulky (i.e., no mass greater than 10 cm in diameter), a short course of chemotherapy (3-4 cycles) followed by radiation therapy to the affected area is appropriate. Patients with bulky stage II, stage III or stage IV disease should be treated with a full course (6-8 cycles) of chemotherapy [7,8]. The type of regimen to use is slightly easier to decide in the situation of a newly-diagnosed diffuse large B-cell lymphoma because randomized trials have been conducted showing that no regimen is superior to CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). Even for those regimens that have shown equal efficacy, CHOP has shown less toxicity [15].

In this patient, though, several poor prognosis features are encountered. First, one has to consider that he has a transformed diffuse large B-cell lymphoma. Transformed diffuse large B-cell lymphomas have historically been associated with a grim prognosis. However, recent data suggests that some of these patients may fare similarly to patients with *de novo* diffuse large B-cell lymphomas. For instance, patients with limited disease who have not previously been treated can experience prolonged survival with conventional therapy. Patients with chemosensitive disease (disease that responds to chemotherapy) should be considered for high dose therapy with autologous stem cell rescue [10].

An important point to keep in mind is that patients with transformed diffuse large B-cell lymphoma may experience a complete remission of the large cell component but remained plagued with the follicular component (i.e., late relapses of the follicular lymphoma may not be altered by the treatment of the diffuse large B-cell lymphoma component).

One can also consider other risk factors that have been proposed for *de novo* diffuse large B-cell lymphomas. This patient has an advanced stage, age over 60 and an elevated LDH. These characteristics place him in a high-intermediate risk group within the International Prognostic Index (IPI) (Table 5). The IPI was developed to assist clinicians in stratifying patients into risk groups. It correlates well with survival [16,17]. Patients in the high-risk group do poorly and, in general, need to be considered for more aggressive and novel therapies.

This patient's high-risk features mandate that other therapy beyond a full course of combination therapy be performed. Patients with *de novo* diffuse large B-cell lymphoma who relapse and have chemosensitive disease benefit from high-dose therapy and autologous stem cell rescue [18]. Although not considered standard, some investigators propose going directly to high-dose therapy and autologous transplant for patients with high-risk features. Whether these observations apply to transformed diffuse large B-cell lymphomas is yet to be determined.

This patient's situation is very difficult. He has relapsed twice (the second time with a transformed diffuse large B-cell lymphoma) and has been treated once already. This makes him unlikely to have a prolonged response to standard systemic therapy. However, it is unclear that proceeding directly to high-dose therapy is the most prudent approach. One option would be to administer 2 to 3 cycles of CHOP. If he has a response (i.e., chemosensitive disease), an autologous transplant could then be offered. It should be noted that autologous transplants can be performed safely in the absence of significant comorbidity with a treatment-related mortality less than 5% in experienced centers. At this point, an allogeneic transplant would be a strong consideration.

Table 5. International prognostic index [16]

Risk group	*Risk factors**	*5-year disease-free survival rate (%)*
Low	0-1	73
Low-Intermediate	2	51
High-Intermediate	3	43
High	4-5	26

*Risk factors: age >60 years, serum LDH above normal, performance status 2-4, stage III or IV, extranodal involvement at more than one site

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Recommended reading:

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