Non-Hodgkin lymphoma: the clinician's perspective—a view from the receiving end

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Optimal treatment of non-Hodgkin lymphoma depends on establishing an accurate diagnosis and determining the stage or anatomic extent of the lymphoma. With this information, the treating clinician can assign the lymphoma to a subgroup characterized by expected natural history: indolent, aggressive, acute leukemia-like or viral, which generally reflects the typical behavior of the disease unmodified by treatment and indicates the urgency with which intervention must be offered. Finally, a number of special circumstances and problems posed by specific lymphomas must be anticipated and the therapeutic plan altered to accommodate them. After primary treatment, special secondary events such as transformation to more aggressive histologic types must be recognized and the treatment plan must be altered to address these events. This article reviews standard diagnostic grouping of lymphomas, special problems encountered during primary diagnosis and subsequent clinical evolution and emphasizes the cooperative interaction between the hematopathologist and the treating clinician that underlies optimal management.

When asked to assess and treat a patient with a non-Hodgkin lymphoma, the clinician must consider specific information about the disease, its extent and the patient's physical condition to plan optimal treatment. After reviewing the available referral data, the clinician initiates an orderly search to determine the patient's status and disease stage. This essential information is shown in Table 1.

A standard treatment plan crucially relies on an accurate histologic diagnosis. If not already available, an adequate biopsy of involved tissue must be obtained. Most desirable is an excisional or incisional biopsy with adequate material for detailed immuno-histochemical, cytogenetic and flow cytometric study.[1–3] In exceptional circumstances, such as clinical urgency or patient frailty, multiple core biopsies may be substituted. Aspiration cytology is inadequate for definitive diagnosis and can only provide a rough guide to a probable diagnosis. It should not be relied on for primary diagnosis if avoidable. Later in this article, we address several special aspects of initial histopathologic diagnosis of lymphoid cancer that also guide choice of treatment.

In contrast to the complexity of classification, the staging of NHL is straightforward. Patients can be divided into two groups on the basis of Ann Arbor stage,[4] bulk or size of tumor and presence of B symptoms (Table 2).

What does the clinician do: treatment choice

Clinicians initially group the lymphomas into major subgroups that reflect their typical behavior if not treated, that is, their unmodified natural history: indolent, aggressive, very aggressive or acute leukemia-like and virally induced. In this sense, the indolent lymphomas typically threaten a patient's life over years, the aggressive lymphomas in months and the leukemia-like lymphomas in weeks. This subgrouping is very useful in determining the basic treatment plan and the urgency with which it must be started. Table 3 shows the adult lymphomas arranged by major treatment-oriented subtype using the nomenclature of the WHO classification.[5]

Treatment approach to non-Hodgkin lymphoma, by major subgroup, with associated exceptions

Indolent Lymphoma

Except for the uncommon (<10%) patients with proven limited stage disease, patients with indolent

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Table 1 Essential information needed to formulate a treatment plan for a patient with lymphoid cancer

1. History searching for constitutional symptoms, localized pain or obstructive symptoms.
2. Physical examination searching for lymphadenopathy, palpable masses, abdominal organomegaly or focal neurologic signs.
3. Computed tomographic (CT) scan of the neck, chest, abdomen and pelvis.
4. Fluorodeoxyglucose positron emission tomographic (FDG-PET)/CT whole body scan for all lymphomas except marginal zone, small lymphocytic/chronic lymphocytic leukemia, lymphoplasmacytic lymphoma or mycosis fungoides, for which FDG uptake is not a reliable determinant of disease involvement.
5. Complete blood counts, serum creatinine, bilirubin, alkaline phosphatase, lactate dehydrogenase (LDH), protein electrophoresis, calcium.
6. Hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody.
7. Diagnostic biopsy results.
8. Bone marrow biopsy and aspiration.

Additional selectively useful tests

1. Human immunodeficiency virus (HIV) antibody.
2. Human T-cell lymphotropic virus type 1 (HTLV-1) antibody.
3. Cytologic assessment of potentially involved fluids, for example, spinal fluid, ascites, pleural effusion.

Table 2 Stage grouping relevant to treatment planning for non-Hodgkin lymphoma

Limited stage	Advanced stage
Ann Arbor I, II	Ann Arbor III, IV[a]
and	or
Bulk < 10 cm	Bulk > 10 cm
and	or
No B symptoms	B symptoms

[a]In the Ann Arbor staging system[4] stages I and II identify disease confined to one or more lymph node groups all on one side of the diaphragm; stage III to lymph node disease on both sides of the diaphragm; and stage IV to disease that has spread into extranodal sites such as bone marrow, liver, lungs or other sites.

lymphoma usually present with advanced stage disease (>90%).[5] Advanced stage indolent lymphoma is not curable with currently available standard treatment; however, these lymphomas can be managed as chronic diseases with short courses of systemic treatment interrupted by long periods of freedom from symptoms or need for treatment for the large majority of patients. Today, such patients can anticipate a 10-year overall survival >80% for younger patients (age<60 years) and >60% for older patients (age>60 years) and treatment outcomes are steadily improving.[6,7]

Important exceptions. Some specific indolent lymphomas require type-specific treatment.
  1. MALT lymphoma of the stomach
  If coincident infection with *Helicobacter pylori* is present and the lymphoma is localized to the

Table 3 A clinically oriented classification of the lymphomas based on natural history, mode of presentation and immunophenotype using the terminology of the 2008 WHO classification scheme

Type	B cell	T cell
Indolent	Small lymphocytic/CLL Lymphoplasmacytic[a] Follicular, grades 1, 2 or 3A Marginal zone MALT Nodal Splenic	Mycosis fungoides Primary cutaneous anaplastic large cell
Aggressive	Mantle cell Diffuse large cell[b], any subtype B-cell lymphoma, unclassifiable with features intermediate between DLBCL and Burkitt lymphoma	Peripheral T-cell, not otherwise specified Peripheral T-cell, specified Angioimmunoblastic Nasal NK/T-cell-type Subcutaneous panniculitis-like Enteropathy-associated Hepatosplenic Anaplastic large cell
Acute leukemia-like	Lymphoblastic Burkitt 'Double hit' lymphomas (see text)	Lymphoblastic
Viral	Primary effusion (HHV-8 associated)	HTLV-1 associated

Abbreviations: HHV-8, human herpes virus type 8; HTLV-1, human T-cell lymphotropic virus type 1.
[a]Formerly plasmacytoid small lymphocytic ± IgM paraprotein (Waldenström's macroglobulinemia).
[b]Immunoblastic, primary mediastinal, T-cell-rich B-cell, intravascular, testicular, primary effusion and primary CNS subtypes.

stomach and peri-gastric lymph nodes, treatment with antibiotics and H2 blockers can eliminate the organism-related antigenic stimulus and the lymphoma may regress permanently.[8,9] This is quite unlikely to happen if *t*(11;18) is present, which testing should be included in processing of gastric MALT lymphomas.[10]
  2. Splenic marginal zone lymphoma
  Splenectomy is often the best choice of primary treatment of splenic marginal zone lymphoma because splenectomy:[11,12]

a Provides a firm diagnosis.
b Eliminates >90% of the total body tumor burden in one simple step.
c Corrects associated cytopenias, allowing other systemic treatments to be given.
d Has little consequence for the patient because full splenic function has already been lost because of infiltration by the lymphoma.

  3. Mycosis fungoides
  This uncommon T-cell lymphoma of the skin typically pursues a very indolent course and is best treated with a collection of remedies specific to the entity including skin irradiation, topical chemotherapy, psoralen-associated ultraviolet

exposure, bexarotene, interferon and histone deacetylase inhibitors.[13]

Aggressive Histology Lymphoma

In contrast to the indolent lymphomas the working assumption for the aggressive histology lymphomas is that they can be cured, with the major exception of mantle cell lymphoma. Thus, for diffuse large B-cell lymphoma (DLBCL), in all its subtypes, and peripheral T-cell lymphomas (PTCLs) of both specific types and otherwise unclassifiable type treatment programs including multi-agent chemotherapy of short duration + radiation for limited stage disease and multi-agent chemotherapy of longer duration for advanced stage disease are standard. When the aggressive lymphoma expresses CD20, as is typical for most but not all of the B-cell aggressive histology lymphomas, rituximab is added. Cure rates vary by stage and the presence of well-defined prognostic factors. Approximately 75% of patients with limited stage[14,15] and about 60% of patients with advanced stage aggressive histology lymphoma can be cured with these approaches.[16] For those with advanced stage disease, likelihood of cure is linked to the presence of well-defined prognostic factors. For B-cell aggressive histology lymphoma if one assigns a point for each of the following: age > 60 years; performance status 2 or greater; lactate dehydrogenase (LDH) > normal; > 1 extranodal site of disease; and Ann Arbor stages III or IV[17] and takes into consideration the favorable impact of rituximab, likelihood of cure is approximately 90% for an IPI score of 0, 80% for a score of 1 or 2 and 55% for a score of 3–5.[18] The corresponding outcomes for the PTCLs are about 1/2 of those for otherwise matched B-cell lymphoma.[19,20]

Important exceptions. Some aggressive histology lymphomas have a different outcome or require a different treatment approach:

1. Mantle cell lymphoma

Mantle cell lymphoma constitutes about 6% of all non-Hodgkin lymphomas in North America and is importantly distinct from the other aggressive histology lymphomas in almost always presenting as advanced stage disease with frequent GI and/or bone marrow involvement and not being curable with standard treatment programs, although similar chemotherapy regimens are usually employed.[21] In addition, about 5–10% of patients present with an indolent variety of mantle cell lymphoma, which is characterized by a particularly low proliferation rate and which may be more appropriately managed with techniques used for indolent lymphoma.[22]

2. Nasal T/NK type PTCL

Nasal T/NK type PTCL is uniquely resistant to standard lymphoma chemotherapy and standard dose radiation used for lymphomas.[23,24] Patients with localized disease require high-dose radiation, a dose similar to that used for nasopharyngeal carcinoma. Patients with advanced stage disease have a particularly poor prognosis and should be considered for experimental treatments.[25]

3. Anaplastic large cell lymphoma (ALCL)

ALCL can be divided into ALK-positive and ALK-negative varieties.[26] ALK-positive ALCL is the exception among PTCLs in being curable at least as often as is seen in otherwise stage and age-matched B-cell aggressive histology lymphomas. ALK-negative ALCL shares the worse prognosis associated with the rest of the PTCLs. In addition, it has now become both diagnostically and clinically imperative to determine both CD30-positivity and ALK-positivity for all ALCLs because of the arrival of two new effective targeted agents, brentuximab vedotin,[27] which targets CD30 and crizotinib, which targets ALK.[28]

Leukemia-Like Lymphomas

This designation, leukemia-like, is of my own coinage but I have found it quite useful when teaching because it communicates the rapidity with which these diseases can progress; the high likelihood of bone marrow and peripheral blood involvement if not already present at diagnosis; the high likelihood of CNS involvement; the necessity to use high-dose chemotherapy regimens, often with hematopoietic stem cell transplantation; and the close association of these diseases with well-defined adult leukemias (Burkitt lymphoma and Burkitt leukemia; lymphoblastic lymphoma and T-cell adult acute lymphoblastic leukemia).[29–33]

Virus-Associated Lymphomas

Two lymphomas seen in adults are known to be causally associated with specific viruses. Adult T-cell leukemia/lymphoma is a T-cell lymphoma that is caused by human T-cell lymphotropic virus type 1. This rare neoplasm is seldom encountered in North America and its natural history can vary substantially ranging from an indolent form to one that presents with crescendo disease and very poor prognosis.[34,35] Primary effusion lymphoma (PEL) is a B-cell lymphoma that presents with malignant pleural, peritoneal and pericardial effusions, is most often, but not exclusively, seen in patients with adult immunodeficiency syndrome (AIDS) and human immunodeficiency virus (HIV) infection and is caused by human herpes virus type 8.[36] PEL is relatively treatment resistant but can be cured with regimens appropriate for aggressive B-cell lymphomas although rituximab is not useful as this lymphoma does not express CD20.

What special problems does the clinician face

Certain special problems can arise when managing lymphomas and discussion between the oncologist and the pathologist can be particularly helpful in addressing them.

Histologic Transformation

Annually about 3% of patients initially diagnosed with indolent (follicular, small lymphocytic, lymphoplasmacytic or marginal zone) lymphoma develop a clinically significant second lymphoma of aggressive, usually large cell, type that presumably originates from the indolent lymphoma and often initially appears in a localized site. The secondary lymphoma is referred to as transformed lymphoma and the event, histologic transformation.[37,38] However, in about 5% of lymphomas this event has occurred before diagnosis and when this is recognized it is referred to as discordant or composite lymphoma. Development of histologic transformation is almost always heralded by at least one of the following:

a Rapid local progression of lymph nodes at one site discordant with the disease elsewhere.
b Progression at an unusual extranodal site such as the CNS, lungs, bone or soft tissue.
c Sudden rise in LDH.
d Hypercalcemia.
e Onset of B symptoms without obvious change in apparent disease extent.[38]

Treatment of histologic transformation (or discordance) requires an approach appropriate for the type and extent of the more aggressive histologic type.[38]

Bone Marrow ± Peripheral Blood Involvement with B-Cell Lymphoma

Patients with DLBCL may have coincident involvement of the bone marrow of one of two types: the DLBCL or one of the indolent B-cell lymphomas, with major clinical consequences.[39] When coincident DLBCL is present both at the primary site and in the bone marrow, 5–10% of patients have or later develop CNS involvement. Such patients should be considered for prophylactic CNS treatment with high-dose methotrexate or intrathecal chemotherapy although at present firm evidence that such an intervention reduces risk of CNS relapse is lacking. When the marrow involvement is with indolent lymphoma the prognosis is considerably better and there is no associated risk of CNS disease.

Paranasal and Base of Skull Sinus Presentation

When lymphoma develops in one of the frontal, maxillary, ethmoid and sphenoid sinuses it is almost always DLBCL and has a strong tendency to cause local destruction, to invade across natural anatomic barriers into the CNS and to metastasize systemically. As this lymphoma develops within the porous structure of the bones at the base of the skull next to the brain it has a tendency to spread to the CNS with estimated rates between 0 and 50% making intrathecal chemotherapy an essential component of treatment.[40]

Testicular Lymphoma

Testicular lymphoma is almost always DLBCL and several special aspects must be considered in treatment planning including a tendency to develop disease in the opposite testicle and, at least in cases presenting with stages III or IV disease, an increased risk of CNS involvement. Patients should be treated with multi-agent chemotherapy followed by involved region irradiation including irradiation of the entire scrotal contents (opposite testicle). CNS prophylaxis is probably not necessary for those presenting with stage IAE or IIAE low bulk disease but should be offered to those with more advanced stage disease.[41]

CNS Lymphoma

Malignant lymphoma may involve the central nervous system in one of three different patterns: metastatic spread to the brain, metastatic spread to the leptomeninges or primary parenchymal disease within the brain. Metastatic spread of lymphoma to cause a solid lesion within the brain is a rare complication of systemic lymphoma of large cell or other aggressive histologic subtype. When isolated brain metastases occur, the use of brain irradiation or high-dose methotrexate can be curative. The more usual mode of metastatic spread to the CNS, involvement of the leptomeninges, is only rarely, if ever, curable. Challengingly, prevention of spread to the CNS using prophylactic CNS treatment is seldom, if ever, effective at lowering the risk of CNS spread. Primary central nervous system lymphoma is usually isolated in the brain and presents as a mass lesion with either focal neurologic symptoms or global cerebral dysfunction with or without headache.[42–54] Most cases in the immunocompetent population are DLBCL and seldom associated with Epstein–Barr virus (EBV); those seen in patients with AIDS or receiving immunosuppressant medications to preserve a transplanted organ are evenly split between large cell and Burkitt-like types and are frequently associated with EBV. Currently, the standard of care for primary CNS lymphoma is high-dose methotrexate in the younger population with good renal function, otherwise, whole brain irradiation.

Eye Lymphoma

Malignant lymphoma involves the structures of the eye in at least two quite distinct patterns.[55–58] The most common presentation is in the peri-orbital soft tissues, particularly the conjunctival mucosal surfaces and the lacrimal gland. Most are mucosa-associated lymphoid tissue lymphomas (MALTs) or, less commonly, follicular lymphoma. Radiation is potentially curative in the majority who present with localized disease.[55–57] Results from Europe contrast with those from North America in showing that peri-orbital soft tissue lymphoma in Europe is often associated with *Chlamydia psittaci* but this has not been found in North America. When *C. psittaci* is present, eradicative treatment with antibiotics may eliminate the lymphoma, a situation analogous to that of *H. pylori* and gastric MALT.

The rarest presentation of lymphoma involving the eye is intraocular[56] and can be quite difficult to diagnose. Although almost all are DLBCL they often pursue a more indolent course than is seen with other sites of DLBCL and are frequently mislabeled chronic uveitis or unexplained vitritis for months or even years before diagnosis is made. The diagnosis is best established by vitrectomy performed when the patient has been off corticosteroids for at least several weeks. Peculiarities of the natural history of intra-ocular lymphoma include its tendency to be bilateral, which occurs in at least 50% of the cases, and its frequent association with brain or leptomeningeal involvement, also seen in at least 50% of the cases. Irradiation is the mainstay of treatment for unilateral intra-ocular lymphoma. Bilateral intra-ocular lymphoma or intra-ocular lymphoma seen in association with brain involvement should be treated the same as primary CNS lymphoma.

Lymphoma in Association with Immunodeficiency Including AIDS

Recipients of organ transplants have an increased risk of developing NHL, predominantly large cell, immunoblastic or Burkitt type and are usually referred to as post-transplant lymphoproliferative disorder (PTLD). These are often associated with EBV and can be difficult to treat successfully. Treatment includes reduction of immunosuppression to the absolute minimum necessary to maintain the transplant. If the lymphoma presentation is not life-threatening, treatment with rituximab alone can be used and is successful in about 50% of patients. Life-threatening or rituximab-resistant PTLD should be treated with multi-agent chemotherapy.[59]

Analogous to the situation with PTLD when lymphoma arises in patients with HIV effective restoration of more nearly normal immunocompetence using highly active anti-retroviral agents plus standard regimens for the type, stage and sites of the lymphoma provides a high expectation of successful control.[60]

Follicular Lymphoma

Two situations involving follicular lymphoma can prove particularly challenging: follicular lymphoma, grade 3 and follicular lymphoma compositely or discordantly present with DLBCL. Many clinicians consider follicular lymphoma, grade 3A to be part of the spectrum of ordinary follicular lymphoma and group such patients with those who have follicular lymphoma, grades 1–2. These same clinicians, however, usually regard follicular lymphoma, grade 3B to be more similar to DLBCL and offer treatment appropriate for DLBCL. Thus, careful distinction between these two types of follicular lymphoma, grade 3A *vs* 3B is of importance to these clinicians and a very relevant aspect that should be clarified by the pathologist.[61]

A minority of lymphomas presenting as DLBCL may have a component of follicular lymphoma in the same diagnostic lymph node biopsy. The most appropriate designation for such lymphomas is DLBCL with areas of follicular lymphoma. Such a designation informs the clinician that the disease in question is a variant of DLBCL and should be managed using the same principles as for that lymphoma.

Dual Translocation or 'Double-Hit' Lymphoma

Follicular lymphoma is almost always associated with *t*(14;18), which leads to dysregulation and inappropriate overexpression of BCL2 and subsequent blockage of apoptosis. Similarly, Burkitt lymphoma is associated with *t*(8;14), which leads to constitutive overexpression of MYC and hyperproliferation. The occurrence of both in the same lymphoma leads to coincidentally blocked apoptosis and hyperproliferation-inducing treatment resistance and a very aggressive clinical course.[62,63] Such dual translocation or 'double-hit' lymphomas may arise *de novo* or as a transformation event from indolent lymphoma. In either case, rapid recognition is crucial because standard regimens appropriate for indolent lymphoma or DLBCL are ineffective. The simple coincidence of *t*(14;18) and *t*(8;14) may not be sufficient to cause this problem. Expression of both oncogenes, *BCL2* and *MYC*, seems to be necessary.[63] In practice, demonstration of overexpression of both protein products, BCL2 and MYC, is the most reliable way to identify the 'double-hit' lymphomas that require escalation of treatment intensity to such regimens as high-dose chemotherapy and hematopoietic stem cell transplantation.

Summary

Optimal management of the non-Hodgkin lymphomas requires close and continuous collaboration between the oncologist treating the patient and the hematopathologist assessing biopsy specimens and

laboratory results. The oncologist starts with the diagnosis issued by the hematopathologist, conducts a thorough staging assessment to determine the extent of disease and formulates a plan predicated on the diagnosis, stage and co-morbid conditions of the patient. This collaboration is strengthened and facilitated when both the oncologist and the hematopathologist appreciate both the standard diagnoses and their natural history and the exceptions seen within each broad category of lymphoma, indolent, aggressive, leukemia-like and viral. Indeed, often the most important aspect that the hematopathologist can communicate to the clinician lies in the nuances and special exceptions that emerge when extensive immunohistochemical, cytogenetic, flow cytometric and now genomic analyses have been completed. Patients are best served when the collaboration between the oncologist and the hematopathologist is collegial, interactive and continuous throughout the management of the patient from primary diagnosis through relapses, if they occur, and as disease responds to or demonstrates resistance to therapeutic interventions.

Disclosure/conflict of interest

The author declares no conflict of interest.

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