NON-HODGKIN'S LYMPHOMAS – A MEDICAL UNDERWRITING PERSPECTIVE

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Non-Hodgkin's Lymphomas are tumors of lymphoid origin with the exception of Hodgkin's Lymphoma and lymphoid leukemias. This includes a broad spectrum of malignant lymphomas with differing natural histories and prognoses. There have been several attempts to classify these diseases, but none satisfactory. As a result, there are several classifications in use. Therefore, Non-Hodgkin's Lymphomas (NHL) are, for most physicians, a difficult group of diseases to comprehend.

It is the intent of this discussion to help obtain a working knowledge of the classification systems, to divide them into groups with similar prognoses for underwriting purposes and to provide some understanding of their natural history. This will not be a comprehensive treatise on Non-Hodgkin's Lymphomas as that is available in many standard texts of Hematology or Medical Oncology.

Malignant lymphomas usually present as lymph node enlargement, hepatosplenomegaly, or involvement of extranodal lymphoid tissue located in various parts of the body. Hodgkin's Lymphoma primarily involves the lymph nodes. In contrast, NHLs involve the extranodal lymphoid tissues in a fourth of the cases.[2] There may also be systemic symptoms such as fever, weight loss and sweats.

A complete and accurate pathological diagnosis is an essential first step in the determination of prognosis and treatment of NHL. Making a pathological diagnosis in these tumors is a complex task and involves the use of specialized studies. Consequently, most general pathologists obtain consultations from hematopathologists before rendering a final opinion.

As indicated earlier, there has not been a good system of classification for these tumors. The knowledge in this field has been evolving over the decades and several classifications have been devised in an attempt to make better decisions on treatment and determine prognoses. As a result, there have been six well described histopathological classifications in use, each claiming superiority over others, making comparison of clinical studies difficult. The Non-Hodgkin's Lymphoma Pathological Classification Project, a unique multi institutional study, was planned and sponsored by The National Cancer Institute in an attempt to resolve these issues.[1] The result is A Working Formulation of Non-Hodgkin's Lymphomas for Clinical Usage designed as a means of translating among the various systems and to facilitate comparisons of clinical studies. Table 1 summarizes their recommendations.

The next step in assessing prognosis is to detemine the extent of spread or stage of the tumor. The Ann Arbor Staging system is the generally accepted standard used for all malignant lymphomas (Table 2).[13] In this staging system the patient is assigned a clinical and pathological stage. To determine the clinical stage, the clinician considers the results of the original biopsy, history, physical examination, laboratory studies and all X-ray and scanning procedures. In addition, the absence (A) or presence (B) of systemic symptoms such as fever, sweats or weight loss is noted. The pathological stage is determined from the results of additional staging procedures such as bone marrow and liver biopsies, laparotomy and splenectomy.[13] This staging system is invaluable in determining prognoses and in planning treatment in Hodgkin's Lymphoma. Its usefulness in NHL, however, is more limited as you will realize from later discussions.

Table 2

The Ann Arbor Staging Classification[13]

Stage I:	Involvement of a single lymph node region (I) or single extralymphatic site (IE)
Stage II:	Involvement of two or more lymph node regions on the same side of the diaphragm (II), which may also include the spleen (IIS), localized extralymphatic involvement (IIE), or both (IISE), if confined to the same side of the diaphragm.
Stage III:	Involvement of lymph node regions on both sides of the diaphragm (III), which may also include the spleen (IIIS), localized extralymphatic involvement (IIIE), or both (IIISE)
Stage IV:	Diffuse or disseminated involvement of extralymphatic sites (e.g., bone marrow, liver, or multiple pulmonary metastases)

The modalities available for the treatment of NHL are similar to those used in Hodgkin's Lymphoma and include systemic chemotherapy, radiotherapy, immunotherapy and surgery. The treatment of NHLs, however, is more individualized, depending on the histologic type and stage of the disease, and is continuing to evolve with advances in basic knowledge about lymphocytes and the immune system. Several chemotherapeutic agents (Table 3) are available for the treatment of NHLs and are used as single agents or in combination (table 4). Radiotherapy, as in the case of Hodgkin's Lymphoma, is also used alone or in combination with chemotherapy. Surgery is the primary mode of therapy in gastrointestinal lymphomas. Immunotherapy in NHL is still investigational and is not widely used.

Table 1

Working Formulation of Non-hodgkin's Lymphoma for Clinical Usage*

Working Formulation	BNLI**	Dorfman	Kiel	Lukes-Collins	Rappaport	WHO
LOW GRADE						
A. Malignant lymphoma small lymphocytic (SL)	diffuse, lymphocytic, well differentiated (small round lymphocyte)	small lymphocytic	lymphocytic, CLL and lymphoplasmacytic/ lymphoplasmacytoid	small lymphocytic and plasmacytoid lymphocytic	lymphocytic, well differentiated	lymphocytic
B. Malignant lymphoma, follicular, predominantly small cleaved cell (FSC)	follicular lymphoma, follicle cells, predominantly small	follicular, small lymphoid	centroblastic-centrocytic (small) follicular	small cleaved follicular center cell (FCC), follicular or follicular and diffuse	nodular, poorly differentiated lymphocytic	nodular prolymphocytic
C. Malignant lymphoma, follicular, mixed small cleaved and large cell (FM)	follicular lymphoma, follicle cells, mixed small and large	follicular, mixed small and large lymphoid	centroblastic-centrocytic (small), follicular	small cleaved FCC, follicular; also large cleaved FCC, follicular	nodular, mixed lymphocytic-histiocytic	nodular, prolymphocytic-lymphoblastic
INTERMEDIATE GRADE						
D. Malignant lymphoma, follicular, predominantly large cell (FL)	follicular lymphoma, follicle cells, predominantly large	follicular, large lymphoid	centroblastic-centrocytic (large), follicular	large cleaved and/or noncleaved FCC, follicular	nodular histiocytic	nodular, prolymphocytic-lymphoblastic.
E. Malignant lymphoma, diffuse small cleaved cell (DSC)	diffuse lymphocytic, intermediate differentiation (small follicle lymphocyte)	diffuse atypical small lymphoid	centrocytic, small	small cleaved FCC, diffuse	diffuse lymphocytic, poorly differentiated	diffuse prolymphocytic
F. Malignant lymphoma, diffuse, mixed small and large cell (DM)	diffuse, mixed small lymphoid and large cell (mixed follicle cells)	diffuse mixed small and large lymphoid	centroblastic-centrocytic, diffuse; and lymphoplasmacytoid, polymorphic	small cleaved, large cleaved, or large non-cleaved FCC, diffuse	diffuse mixed lymphocytic-histiocytic	diffuse prolymphocytic lymphoblastic
G. Malignant lymphoma, diffuse, large cell (DL)	diffuse undifferentiated large cell (large lymphoid cell)	diffuse large lymphoid	centroblastic-centrocytic (large), diffuse; centrocytic (large), and centroblastic, diffuse	large cleaved or non-cleaved FCC, diffuse	diffuse histiocytic	diffuse lymphosarcoma, prolymphocytic-lymphoblastic
HIGH GRADE						
H. Malignant lymphoma, large cell, immunoblastic (IBL)	diffuse undifferentiated large cell (large lymphoid cell), plasma cell (extramedullary plasma cell)	diffuse large lymphoid	immunoblastic and T-zone lymphoma	immunoblastic sarcoma, T-or B-cell type	diffuse histiocytic	diffuse lymphosarcoma, immunoblastic
I. Malignant lymphoma, lymphoblastic (LBL)	diffuse lymphocytic poorly differentiated (lymphoblast); convoluted cell mediastinal lymphoma	lymphoblastic, convoluted/non-convoluted	lymphoblastic convoluted, or unclassified	convoluted T-cell	lymphoblastic convoluted/non-convoluted	diffuse lymphosarcoma, lymphoblastic
J. Malignant lymphoma, small noncleaved cell (SNC)	diffuse lymphocytic, poorly differentiated (lymphoblast), non-Burkitt's and Burkitt's tumor	Burkitt's lymphoma	lymphoblastic, Burkitt's type and other B-lymphoblastic	small noncleaved follicular center cell	undifferentiated, Burkitt's and non-Burkitt's	Burkitt's tumor

* Modified from National Non-Hodgkin's Lymphoma Pathological Classification Project.1

** British National Lymphoma Investigation Classification

Table 3

Single Agents, Active in Non-hodgkins Lymphoma[13]

Nitrogen mustard	Procarbazine	BCNU
Cyclophosphamide	Prednisone	DTIC
Chlorambucil	Adriamycin	VM-26
Vinblastine	Bleomycin	VP-16-213
Vincristine		

Table 4

Chemotherapy Combinations Active in NHL

COP or CVP	Cyclophosphamide, Vincristine, Prednisone
C-MOPP or COPP	Cyclophosphamide, Vincristine, Procarbazine and Prednisone
CHOP-BLEO	Cyclophosphamide, Adriamycin, Vincristine, Prednisone, and Bleomycin
COP BLAM	Cyclophosphamide, Vincristine, Prednisone, Bleomycin, Adriamycin, and Procarbazine
M-BACOP	Bleomycin, Adriamycin, Cyclophosphamide, Vincristine, Methotrexate, Prednisone and Folinic Acid
COMA	Cyclophosphamide, Methotrexate, Vincristine, and Cytosine Arabinoside

Further discussion of NHLs for the purpose of determining prognoses is best done under the following sub headings.

The Low Grade Lymphomas

The three types which constitute the low grade lymphomas are the small lymphocytic, the follicular small cleaved and follicular mixed.

The low grade NHLs run a prolonged course and are sensitive to therapy, but therapy does not seem to influence long term survival. Therefore, the aim of therapy in low grade lymphomas is palliation rather than cure. Consequently, the minimum amount of therapy needed to control symptoms is used. Thus, single agent chemotherapy, less toxic multi agent combination, like COP or involved field radiation therapy are the treatments of choice depending on the location and extent of disease.

Eighty-one percent of all cases of small lymphocytic type have stage IV disease at the time of diagnosis usually from bone marrow involvement.[3] Approximately 10% of the follicular small cleaved and mixed lymphomas are stage I. The stage I low grade NHL have a 10 year survival probability of 83%(CI 65 to 92). Stage II cases have prognoses closer to III and IV disease. Patients with stages III and IV diseases have survival probabilities of 48%(CI, 37 to 60) and 37%(CI, 29 to 44) respectively.[3]

Those who are in long remissions have better prognoses compared to those who relapse early. Frequently, it is possible to obtain a durable second and third remission in low grade NHL. These lymphomas, however, pursue a more aggressive course and become unresponsive to therapy late in its course and biopsies done at this time usually show diffuse large cell (DL) or immunoblastic (IBL) lymphoma.[4]

The Intermediate and High Grade

These are more aggressive tumors in which prompt and appropriate treatment has a definite impact on outcome. Stage I cases which constitute about 15% of intermediate and high grade tumors receive radiotherapy as the primary treatment. The use of adjuvant combination chemotherapy in this early stage has resulted in substantial improvement in survival.[8] The advanced stages receive histology specific combination chemotherapy and radiotherapy only to areas of bulky disease.

The high and intermediate grade NHLs have a similar prognoses and the various histological sub types are not associated with significantly different prognoses.[5] In a recently reported large follow up of NHL, it was noted that, with appropriate treatment, the diffuse large cell and immunoblastic lymphomas have 10 year survival probabilities of 53% (CI, 39 to 66) for stage I, 27% (CI, 18 to 38) for stage II and 15% (CI,18 to 34) for stages III and IV.3 The stage, presence or absence of bulky disease, LDH and albumin level at diagnosis are predictors of prognosis. Those with bulky disease have high LDH, low albumin and a poor prognosis. These factors are independent of the stage as predictors of outcome. Those who attain complete remission with therapy have a vastly improved prognosis over those who do not.[5]

Relapses in early stage tumors usually occur within the first two to three years after completing treatment. In the advanced stage tumors, the survival curve does not flatten until about five years.[3]

Extranodal Lymphomas

Primary extranodal presentation accounts for approximately 25% of all cases of adult NHL in contrast to about 1% in the case of Hodgkin's Lymphomas.[2] The gastrointestinal and extranodal head and neck presentations account for about two thirds of all extranodal cases. The therapy used is also similar to that used in nodal NHLs. The exception is the case of gastrointestinal lymphomas where surgery is performed to remove bulky disease and to reduce intra-abdominal complications during treatment. Stage for stage the prognoses of extranodal NHLs is identical to that of nodal NHLs of comparable grade and bulk of disease.

Childhood Lymphomas

The lymphomas that typically occur in children and adolescents differ from those common in adults in a number of important respects including origin and distribution of disease, aggressiveness and response to treatment.[9] The majority of the tumors occur in extranodal locations with equal frequencies presenting in the abdomen, mediastinum or the head and neck region. Almost all cases belong to categories of high grade diffuse lymphomas; namely, small non-cleaved cell, lymphoblastic and large cell immunoblastic type. Stage and LDH level, as in adults, are important prognostic indicators in children. Protocol based staging and introduction of histology-specific therapy for advanced stage disease has improved survival markedly in the past decade. Approximately 80% of the children with NHL treated in childhood cancer centers are cured. The relapse hazard is a function of time and varies according to histology. Most relapses occur early, within the first year, in small non-cleaved lymphomas, whereas failures occur after several years in lymphoblastic lymphomas. Nev-

ertheless, the risk of relapse is quite low after five years in these diffuse aggressive high grade lymphomas.[9]

Underwriting Guidelines

There is a significant difference in survival between stage I and all other stages in all grades of NHL. The survival difference between stages II to IV is inconsequential for practical purposes. Once complete remission is achieved, the significance of bulky disease, LDL and albumin level as prognostic indicators decreases. These factors, however, should be taken into account in determining the prognosis in any individual case.

Stage I low grade NHLs in complete remission have a fairly good prognosis. There may be some early indication that some of these cases may be cured. The preponderance of evidence suggests, however, that survival is approximately 10 to 15 years. In view of the short survival even in the best category of low grade NHL, it would be difficult to adequately price for this impairment in those under 60 years of age. Consequently, those 60 years of age and older with stage I low grade lymphomas, can be insured at a total mortality charge in the 200% to 300% range, after they have been in remission for at least two years. All other stages should be lumped together and rated in the high sub-standard category after they have been in complete remission for the same duration. Cessation of all therapy is not critical when evaluating remissions in low grade NHL as cure is not expected. A permanent table rating is appropriate because of the duration of survival and the age group involved.

Many cases of intermediate and high grade lymphomas in long term remission are probably cured. These, like the low grade NHL, are divided into two prognostic groups; namely, stage I and all other stages combined. The stage I cases in complete remission for two years or more after completion of therapy could be insured with flat extras for a period of five years. Those in stages II to IV could similarly be insured after a period of five years or more of complete remission with appropriate flat extras.

The behavior of extranodal lymphomas is similar to that of other adult malignant lymphomas and the same prognostic factors and categories apply.

In the case of childhood lymphomas it is better to assume a more conservative position for the following reasons: most childhood lymphomas are in the advanced stages at the time of diagnosis, there are difficulties in determining insurable interest, and pricing of life insurance for children is difficult. Insurance coverage should only be offered to those free of recurrence for five years or more at a mortality charge in the 150 to 200% range to cover the small number of relapses and long term complications of therapy.

Cases of NHL that fail to achieve complete remission are uninsurable. Moreover, in those who attain complete remission there is a small but significant risk of long term complications resulting from therapy as noted in the long term survivors of Hodgkin's lymphoma.[11] The most significant of these complications is the risk of leukemia-related events and is highest in those receiving a combination of chemotherapy and radiotherapy. This risk peaks at four to six years and decreases to that of a normal population in 10 to 12 years. Therefore, a small additional rating in the 25% to 50% range should be added to cover the first 10 years following multiagent chemotherapy and an even higher rating in the 50 to 100% range for those treated with the combination of chemotherapy and radiotherapy to cover this treatment related mortality.

Conclusion

This has been a subjective analysis and interpretation of available medical literature. A more objective mortality analysis is not feasible because rapid advances in therapy has made most of the available long term survival data irrelevant. In addition, the multiple classification systems in use have made evaluation of any available information difficult. As more long term follow-up information based on The Working Formulation and newer treatments becomes available, a more precise mortality analysis would be warranted.

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