Disease Information

The two main malignant diseases of the lymphoreticular system are non-Hodgkin's lymphoma and Hodgkin's disease. Lymphoma is a general term applied to a heterogeneous group of cancers which develop from lymphoreticular tissue. The lymphoreticular system is part of the immune system. The lymphocyte is the principal cellular component of lymphoid tissue. There are two major populations of lymphoreticular cells, T-cells (lymphocytes processed through the thymus) and B-cells (thymus independent cells). Other cells of the lymphoreticular system include cells of the monocyte macrophage series, reticulum supporting cells and dendritic and interdigitating reticulum cells.

Lymphoreticular cells are distributed throughout the tissues of the body, with the exception of central nervous system tissues. Primary lymphoid organs, which generate lymphoid cells, are the bone marrow and thymus. Secondary lymphoid organs which are populated by differentiated lymphoid cells include the lymph nodes, the spleen and Waldeyer's ring.

Hodgkin's Disease

Hodgkin's disease generally has characteristic Reed-Sternberg cells which distinguish it from non-Hodgkin's lymphomas. The Hodgkin's disease pattern of spread is more predictable and generally more limited than some of the non-Hodgkin's lymphomas. Typical presentation is characterized by painless lymph node enlargement with or without fever, night sweats, or weight loss. The presenting lymphadenopathy is supradiaphragmatic in 90% of the cases. Most patients with Hodgkin's disease present with Ann Arbor Stage I or II disease (please refer to Staging on Page 5). Common sites of distant spread are bone marrow, spleen, and liver.

Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphomas tend to occur more frequently in people over the age of 50. Signs and symptoms for non-Hodgkin's lymphoma are similar to those for Hodgkin's disease. Non-Hodgkin's lymphomas are more likely to present with extensive spread of disease. Common sites of involvement are oropharynx, skin, gastrointestinal tract and bone tissue.

AIDS Lymphoma

During the 1980's researchers noted an increased incidence of B-cell lymphomas in patients with acquired immune deficiency syndrome (AIDS). In 1985, the Center for Disease Control changed its definition of AIDS to include high grade B-cell lymphomas as an indicator of AIDS manifestation. For some patients, lymphoma is the initial presenting diagnosis of AIDS, while in other patients, the appearance of lymphoma occurs relatively late in the AIDS process.

Pathology

Non-Hodgkin's Lymphoma (NHL)

At the present time the World Health Organization (WHO) classification [World Health Organization Classification of Tumours. Lyon, France: IARC Press 2001] is used for lymphoma. A prior pathologic classification, the Working Formulation scheme, categorized tumors as high grade, intermediate grade and low grade.
The Working Formulation was supplanted by the REAL (Revised European American Lymphoma) classification, which distinguished between B-cell and T-cell neoplasms and whose major components are follicular lymphomas and diffuse large B-cell lymphomas. The current WHO classification was based on the REAL system and the term REAL is still used in some older studies.

**Hodgkin's Disease**

The first clinically useful subclassification system of Hodgkin's disease was derived by Jackson and Parker in 1944. This scheme divided Hodgkin's disease into three categories ranging from most favorable to least favorable prognoses. However, most of the cases of Hodgkin's disease occurred in the middle of these three categories; hence further subclassification was needed. Advances were made in 1966 when Lukes, Hicks and Butler published a new scheme which seemed in practice to correlate well with both clinical stage and histologic aggressiveness of the disease. The Lukes and Butler classification scheme, further simplified at the Rye Convention, supplanted this scheme. Today, the World Health Organization (WHO) classification (on Page 3) is widely accepted and used by both pathologists and clinical oncologists.
Classification of Non-Hodgkin's Lymphoma

World Health Organization (WHO) Classification*

**B cell lymphomas**
- Precursor B-lymphoblastic leukemia/lymphoma
- Precursor B-cell acute lymphoblastic leukemia
- B-cell CLL/SLL*
- B-cell prolymphocytic leukemia
- Lymphoplasmacytic lymphoma (immunocytoma)
- Splenic marginal zone B-cell lymphoma
- Hairy cell leukemia
- Plasma cell myeloma/plasmacytoma
- Extranodal marginal zone B-cell lymphoma of MAL** type
- Nodal marginal zone B-cell lymphoma
- Follicular lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma
- Mediastinal large B-cell lymphoma
- Primary effusion lymphoma
- Burkitt lymphoma

**T cell lymphomas**
- Precursor T-lymphoblastic lymphoma/leukemia
- Precursor T-cell acute lymphoblastic leukemia
- T-cell prolymphocytic leukemia
- Large granular lymphocytic leukemia/LGL
- Adult T-cell lymphoma/leukemia
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-type T-cell lymphoma
- Hepatosplenic gamma-delta T-cell lymphoma
- Subcutaneous panniculities-like T-cell lymphoma
- Mycosis fungoides
- Anaplastic large-cell lymphoma
- Peripheral T-cell lymphoma, unspecified
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma

*CLL: Chronic lymphocytic leukemia; SLL: small lymphocytic lymphoma
** MAL: mucosa-associated lymphoid
Hodgkin's Disease (WHO Classification)

- Nodular lymphocyte-predominant Hodgkin lymphoma
- Classical Hodgkin lymphoma
  - Nodular sclerosis Hodgkin lymphoma
  - Lymphocyte rich Hodgkin lymphoma
  - Mixed cellularity Hodgkin lymphoma
  - Lymphocyte depleted Hodgkin lymphoma

Prognostic Factors

Histology and stage are important predictive factors for survival and remission induction. In general, patients with Hodgkin's disease have a better prognosis than those with non-Hodgkin's lymphoma. Among patients with non-Hodgkin's lymphoma, favorable histology is associated with a more indolent clinical course. For both non-Hodgkin's lymphoma and Hodgkin's disease, Ann Arbor Stage I-II has better prognosis than Stage III-IV.

In 1993, the International Non-Hodgkin's Lymphoma Prognostic Factors Project published results of prognostic factor analysis for patients with aggressive non-Hodgkin's Lymphoma. (New England Journal of Medicine, 329(14):987-994, 1993). Clinical factors predictive of survival and progression-free survival and included in the prognostic are as follows: LDH, performance status, stage, age, and number of extra nodal sites.

In 2004, an international group published results of an updated prognostic factor analysis, looking specifically at follicular lymphoma patients. (Blood, 104(5): 1258-1265, 2004). Clinical factors predictive of survival in this subset of NHL patients are: age, Ann Arbor stage, hemoglobin, number of nodal sites, and LDH.


Treatment

In general, for aggressive histology non-Hodgkin's lymphoma, initial treatment is aggressive multiagent chemotherapy; intent is curative. Hodgkin's disease is treated with radiation or chemotherapy, depending on stage, and is curable in the majority of cases. Indolent histology non-Hodgkin's lymphoma is also treated with radiation and/or chemotherapy, depending on stage (chemotherapy for high stage). For all lymphomas, chemotherapy is given after relapse. Bone marrow transplantation may be considered for treatment of refractory disease for patients failing to achieve an initial remission, or for patients with poor prognosis prior to initial treatment.
Monoclonal anti-body therapy for Non-Hodgkin's Lymphoma is now widely used alone or in combination with chemotherapy. The best known example of monoclonal anti-body therapy is Rituximab which is directed to the CD20 antigen expressed on normal and malignant B cells. Other examples of monoclonal antibody treatment for Non-Hodgkin's Lymphoma include ibritumomab tixetan (Zevalin) and tositumomab (BEXXAR). These later two antibodies have radioactive molecules attached to them to direct radiation directly to the cancer cells.

Staging

The Ann Arbor classification, adopted in 1971, was originally designed to stage patients with Hodgkin's disease, but is now used to classify patients with non-Hodgkin's lymphoma as well.

The Ann Arbor system categorizes lymphomas into four stages based on the extent of anatomical involvement. Each stage is designated by a Roman numeral and is subclassified as A or B, indicating the absence (A) or presence (B) of certain systemic symptoms: unexplained weight loss of more than 10% of body weight in the last six months, unexplained fever with temperatures above 38 degrees Celsius, or night sweats.

Further, the Ann Arbor stage is designated as clinical staging only or pathologic staging. Clinical stage includes history and physical examination, laboratory tests, and radiographic evidence, as well as evidence of disease obtained from the initial biopsy. In addition to these methods, pathologic staging includes subsequent biopsy and microscopic examination of liver, bone marrow, spleen and/or abdominal nodes.


**Stage I**
Involvement of a single lymph node region (I) or localized involvement of a single extralymphatic organ or site (I_E).

**Stage II**
Involvement of two or more lymph node regions on the same side of the diaphragm (II), or localized involvement of a single associated extralymphatic organ or site and its regional nodes with or without other lymph node regions on the same side of the diaphragm (II_E).

**Stage III**
Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized involvement of an extralymphatic organ or site (III_E), by involvement of the spleen (III_s), or both (III_E+S).

**Stage IV**
Disseminated (multifocal) involvement of one or more extralymphatic organs with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (non-regional) nodal involvement.