FOURTH EDITION

Cancer Management: A Multidisciplinary Approach

Medical, Surgical, & Radiation Oncology

Edited by

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US Food and Drug Administration

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And the editors of the journal ONCOLOGY

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CHAPTER 30

Non-Hodgkin's lymphoma

Arturo Molina, MD, and Richard D. Pezner, MD

Between 1973 and 1996, the incidence of non-Hodgkin's lymphoma (NHL) rose by 81% in the United States, representing one of the largest increases of any cancer. Although some of this increase may be artifactual, resulting from improved diagnostic techniques and access to medical care, or may be directly related to the development of NHL in 20- to 40-year-old men with human immunodeficiency virus (HIV) infection, an unexpected increase in frequency of NHL has been observed throughout the United States.

The incidence of NHL per 100,000 persons has risen from 9.8 in 1972-1974 to 13.6 in 1992-1996. The increases have been relatively higher in whites, males, and the elderly, and rates have risen more rapidly in rural than urban areas. Similar findings have been reported in other developed countries.

Currently, NHL represents approximately 4.0% of all cancer diagnoses (4.3% in males and 3.7% in females). Estimates from the American Cancer Society indicate that in the year 2000, some 56,800 new cases of NHL will be diagnosed in the United States and approximately 25,700 people will die of this disease.

Epidemiology

Gender The overall incidence of lymphoma is slightly higher in men than women. The incidence rate (per 100,000 population) in 1989 was 56% higher in white males (17.8) than white females (11.4).

Age Except for high-grade lymphoblastic and small noncleaved cell lymphomas, which are the most common types of NHL seen in children and young adults, the median age at presentation for all subtypes of NHL is over 50 years. Low-grade lymphomas account for 37% of NHLs in patients between the ages of 35 and 64 years at diagnosis but for only 16% of cases in those below the age of 35 and are extremely rare in children.

Race Incidence varies by race, with whites at higher risk than blacks and Asian-Americans. Most histologies, particularly low-grade small lymphocytic and follicular lymphomas, are more common in whites than blacks. The incidence of mycosis fungoides is highest in black males and lowest in white females.

Geography Certain endemic geographical factors appear to influence the development of NHL in specific areas.

HTLV-1-associated NHL Human T-cell lymphotrophic virus-1 (HTLV-1)–associated T-cell lymphoma/leukemia occurs more frequently in Japan (Kyushu) and the Caribbean.

Burkitt's lymphoma in Africa The incidence (per 100,000 population) of Burkitt's NHL in Africa (Nigeria and Tanzania) is 5.7-7.6, as compared with 0.1 in the United States. The clinical features of Burkitt's lymphoma in Africa differ from those of cases reported to the American Burkitt's Lymphoma Registry. Etiologic endemic factors include malaria as a source of chronic B-cell antigenic stimulation and Epstein-Barr virus (EBV)–induced immortalization of B-lymphocytes.

Middle East lymphoma or α–chain disease α Heavy-chain disease is a disorder of B-lymphoid cells characterized by diffuse thickening of the small intestine due to a lymphoplasmacytic infiltrate with secretion of incomplete IgA heavy chains. This clinicopathologic entity is rarely encountered in individuals other than those of Mediterranean ethnic origin.

Follicular lymphomas are more common in North America and Europe but are rare in the Caribbean, Africa, China, Japan, and the Middle East.

Peripheral T-cell lymphomas are more common in Europe and China than in North America.

Disease site Malignant lymphomas are a heterogeneous group of neoplasms that usually arise or present in lymphoid tissues, such as lymph nodes, spleen, and bone marrow, but that may arise in almost any tissue. The most frequent sites for extranodal lymphomas, which constitute about 26% of all lymphomas, are the stomach, skin, oral cavity and pharynx, small intestine, and CNS. Although primary CNS lymphoma is rare, there has been a 3-fold increase in incidence, even if patients with HIV infection and other types of immunosuppression are excluded.

Survival The 5-year relative survival rate of patients with NHL increased from 28% between 1950 and 1954 to 49% between 1979 and 1985. These improvements in survival occurred mainly in young adults and children. The potential for cure varies among the different histologic subtypes and is directly related to stage at presentation and response to initial therapy.

Etiology and risk factors

Chromosomal translocations and molecular rearrangements Nonrandom chromosomal and molecular rearrangements play an important role in the pathogenesis of many lymphomas and correlate with histology and immunophenotype (Table 1). The most commonly associated chromosomal abnormality in NHL is the t(14;18)(q32;q21) translocation, which is found in 85% of follicular lymphomas and 28% of higher-grade NHLs. This translocation results in the juxtaposition of the *bcl-2* apoptotic inhibitor "oncogene" at chromosome band 18q21 to the heavy-chain region of the immunoglobulin locus within chromosome band 14q32.

TABLE 1: Correlation of chromosomal abnormalities in NHL with histology, antigen rearrangements, and oncogene expression

Cytogenetic abnormality	Histology	Antigen rearrangement	Oncogene expression
B-cell lymphoma			
t(14;18)(q32;q21)	Follicular (small cleaved, mixed, large cell), diffuse large cell	IgH	*bcl-2*
t(11;14)(q13;q32)	Mantle cell	IgH	*bcl-1*
t(1;14)(p22;q32)	MALT lymphoma	IgH	*bcl-10*
t(11;18)(q21;q21)	MALT lymphoma	IgH	Unknown
t(9;14)(p13;q32)	Lymphoplasmacytic lymphoma	IgH	*PAX-5*
t(14;19)(q32;q13.1)	B-CLL	IgH	*bcl-3*
8q24 translocations	Small noncleaved		*c-myc*
t(8;14)(q24;q32)	(Burkitt's and	IgH	
t(2;8)(p11-12;q24)	non-Burkitt's	Ig-λ	
t(8;22)(q24;q11)	types)	Ig-κ	
(3;22)(q27;q11)	Diffuse (large cell, small cleaved cell)	Ig-κ	*bcl-6 (LAZ-3)*
Trisomy 12	Small lymphocytic, B-CLL		
T-cell lymphoma			
14q11 abnormalities			
inv 14(q11;q32)	Variable	TCR-δ	*tcl-1*
t(11;14)(p13;q11)	T-ALL	TCR-δ	*tcl-2*
t(10;14)(q24;q11)	Variable	TCR-δ	*hox-11 (tcl-3)*
t(1;14)(p32;q11)	T-ALL	TCR-δ	*tcl (tal1, tcl-5)*
7q35 abnormalities			
t(7;9)(q34-36;q32)	T-ALL or lymphoblastic lymphoma	TCR-β	*tcl-4*
t(7;14)(q34-36;q11)	Variable	TCR-β	
t(7;19)(q34-36;q13)	T-ALL	TCR-β	*lyl-1*
t(2;5)(p23;q35)	Anaplastic large cell (Ki-1 positive)		*npm, alk*

alk = anaplastic lymphoma kinase gene; B-CLL = B-cell chronic lymphocytic leukemia; IgH = immunoglobulin heavy chain; Ig-κ = immunoglobulin kappa light chain; Ig-λ = immunoglobulin lambda light chain; *LAZ-3* = *LAZ-3* transcription factor gene; MALT = mucosa-associated lymphoid tissue; *npm* = nucleophosmin gene; T-ALL = T-cell acute lymphocytic leukemia; TCR = T-cell antigen receptor

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