the United States report an estimated 5-year survival rate of 60% in the era of TKIs.

The current high cost of TKI therapies poses two additional considerations. The first are the treatment pathways and guidelines in nations where TKIs may not be affordable by patients or the health care system. In these conditions, there are trends of pathways advocating frontline allogeneic SCT (a one-time cost of $30,000–$50,000) despite the associated mortality and morbidities. The second is the choice of frontline TKI therapy once imatinib becomes available in generic forms (hopefully at much lower annual prices, e.g., $2,000–$10,000). This will depend on the maturing data in randomized studies of second-generation TKIs versus imatinib in relation to important long-term outcome endpoints, particularly survival, but also event-free survival and transformation-free survival.

134 Malignancies of Lymphoid Cells

Dan L. Longo

Malignancies of lymphoid cells range from the most indolent to the most aggressive human malignancies. These cancers arise from cells of the immune system at different stages of differentiation, resulting in a wide range of morphologic, immunologic, and clinical findings. Insights on the normal immune system have allowed a better understanding of these sometimes confusing disorders.

Some malignancies of lymphoid cells almost always present as leukemia (i.e., primary involvement of bone marrow and blood), while others almost always present as lymphomas (i.e., solid tumors of the immune system). However, other malignancies of lymphoid cells can present as either leukemia or lymphoma. In addition, the clinical pattern can change over the course of the illness. This change is more often seen in a patient who seems to have a lymphoma and then develops the manifestations of leukemia over the course of the illness.

BIOLOGY OF LYMPHOID MALIGNANCIES: CONCEPTS OF THE WORLD HEALTH ORGANIZATION CLASSIFICATION OF LYMPHOID MALIGNANCIES

The classification of lymphoid cancers evolved steadily throughout the twentieth century. The distinction between leukemia and lymphoma was made early, and separate classification systems were developed for each. Leukemias were first divided into acute and chronic subtypes based on average survival. Chronic leukemias were easily subdivided into those of lymphoid or myeloid origin based on morphologic characteristics. However, a spectrum of diseases that were formerly all called *chronic lymphoid leukemia* has become apparent (Table 134-1). The acute leukemias were usually malignancies of blast cells with few identifying characteristics. When cytochemical stains became available, it was possible to divide these objectively into myeloid malignancies and acute leukemias of lymphoid cells. Acute leukemias of lymphoid cells have been subdivided based on morphologic characteristics by the French-American-British (FAB) group (Table 134-2). Using this system, lymphoid malignancies of small uniform blasts (e.g., typical childhood acute lymphoblastic leukemia) were called L1, lymphoid malignancies with larger and more variable size cells were called L2, and lymphoid malignancies of uniform cells with basophilic and sometimes vacuolated cytoplasm were called L3 (e.g., typical Burkitt's lymphoma cells). Acute leukemias of lymphoid cells have also been subdivided based on immunologic (i.e., T cell vs B cell) and cytogenetic abnormalities (Table 134-2). Major cytogenetic subgroups include the t(9;22) (e.g., Philadelphia chromosome–positive acute lymphoblastic leukemia) and the t(8;14) found in the L3 or Burkitt's leukemia.

TABLE 134-1 LYMPHOID DISORDERS THAT CAN PRESENT AS "CHRONIC LEUKEMIA" AND BE CONFUSED WITH TYPICAL B-CELL CHRONIC LYMPHOID LEUKEMIA

Follicular lymphoma	Prolymphocytic leukemia (B cell or T cell)
Splenic marginal zone lymphoma	Lymphoplasmacytic lymphoma
Nodal marginal zone lymphoma	Sézary's syndrome
Mantle cell lymphoma	Smoldering adult T-cell leukemia/lymphoma
Hairy cell leukemia	

TABLE 134-2 CLASSIFICATION OF ACUTE LYMPHOID LEUKEMIA (ALL)

Immunologic Subtype	% of Cases	FAB Subtype	Cytogenetic Abnormalities
Pre-B ALL	75	L1, L2	t(9;22), t(4;11), t(1;19)
T-cell ALL	20	L1, L2	14q11 or 7q34
B-cell ALL	5	L3	t(8;14), t(8;22), t(2;8)

Abbreviation: FAB, French-American-British classification.

Non-Hodgkin's lymphomas were separated from Hodgkin's lymphoma by recognition of the Sternberg-Reed cells early in the twentieth century. The histologic classification for non-Hodgkin's lymphomas has been one of the most contentious issues in oncology. Imperfect morphologic systems were supplanted by imperfect immunologic systems, and poor reproducibility of diagnosis has hampered progress. In 1999, the World Health Organization (WHO) classification of lymphoid malignancies was devised through a process of consensus development among international leaders in hematopathology and clinical oncology. The WHO classification takes into account morphologic, clinical, immunologic, and genetic information and attempts to divide non-Hodgkin's lymphomas and other lymphoid malignancies into clinical/pathologic entities that have clinical and therapeutic relevance. This system is presented in Table 134-3. This system is clinically relevant and has a higher degree of diagnostic accuracy than those used previously. The possibilities for subdividing lymphoid malignancies are extensive. However, Table 134-3 presents in bold those malignancies that occur in at least 1% of patients. Specific lymphoma subtypes will be dealt with in more detail below.

Lymphomas occurring in fewer than 1% of patients with lymphoproliferative diseases are discussed in Chap. 135e, and lymphomas associated with HIV infection are discussed in Chap. 226.

GENERAL ASPECTS OF LYMPHOID MALIGNANCIES

ETIOLOGY AND EPIDEMIOLOGY

The relative frequency of the various lymphoid malignancies is shown in Fig. 134-1. Chronic lymphoid leukemia (CLL) is the most prevalent form of leukemia in Western countries. It occurs most frequently in older adults and is exceedingly rare in children. In 2014, 15,720 new cases were diagnosed in the United States, but because of the prolonged survival associated with this disorder, the total prevalence is many times higher. CLL is more common in men than in women and more common in whites than in blacks. This is an uncommon malignancy in Asia. The etiologic factors for typical CLL are unknown.

In contrast to CLL, acute lymphoid leukemias (ALLs) are predominantly cancers of children and young adults. The L3 or Burkitt's leukemia occurring in children in developing countries seems to be associated with infection by the Epstein-Barr virus (EBV) in infancy. However, the explanation for the etiology of more common subtypes of ALL is much less certain. Childhood ALL occurs more often in higher socioeconomic subgroups. Children with trisomy 21 (Down's syndrome) have an increased risk for childhood ALL as well as acute myeloid leukemia (AML). Exposure to high-energy radiation in early childhood increases the risk of developing T-cell ALL.

The etiology of ALL in adults is also uncertain. ALL is unusual in middle-aged adults but increases in incidence in the elderly. However, AML is still much more common in older patients. Environmental exposures, including certain industrial exposures, exposure to agricultural chemicals, and smoking, might increase the risk of developing