Table 13-9 Clinical Staging of Hodgkin and Non-Hodgkin Lymphomas (Ann Arbor Classification)

Stage	Distribution of Disease
I	Involvement of a single lymph node region (I) or a single extralymphatic organ or site (IE)
II	Involvement of two or more lymph node regions on the same side of the diaphragm alone (II) or localized involvement of an extralymphatic organ or site (IIE)
III	Involvement of lymph node regions on both sides of the diaphragm without (III) or with (IIIE) localized involvement of an extralymphatic organ or site
IV	Diffuse involvement of one or more extralymphatic organs or sites with or without lymphatic involvement
All stages are further divided on the basis of the absence (A) or presence (B) of the following symptoms: unexplained fever, drenching night sweats, and/or unexplained weight loss of greater than 10% of normal body weight.	

Data from Carbone PT, et al: Symposium (Ann Arbor): Staging in Hodgkin's disease. *Cancer Res* 31:1707, 1971.

incidence of secondary tumors, particularly acute myeloid leukemia. These sobering results spurred the development of current treatment regimens, which minimize the use of radiotherapy and employ less genotoxic chemotherapeutic agents; as a result, the incidence of secondary tumors appears to have been reduced markedly, without any loss of therapeutic efficacy. Anti-CD30 antibodies have produced excellent responses in patients with disease that has failed conventional treatments and represent a promising targeted therapy.

KEY CONCEPTS

Hodgkin Lymphoma

- Unusual tumor consisting mostly of reactive lymphocytes, macrophages, eosinophils, plasma cells and stromal cells mixed with rare tumor giant cells called Reed-Sternberg cells and variants
- Two broad types, classical (which has several subtypes) and lymphocyte predominant, which are distinguished based on morphologic and immunophenotypic grounds
- Reed-Sternberg cells of classical types make multiple cytokines and chemokines that influence the host response, and the host response in turn makes factors that support the growth of the tumor cells
- Classical forms are frequently associated with acquired mutations that activate the transcription factor NF-κB and with EBV infection
- Lymphocyte predominance type expresses B cell markers and is not associated with EBV

Myeloid Neoplasms

The common feature of this heterogeneous group of neoplasms is an origin from hematopoietic progenitor cells. These diseases primarily involve the marrow and to a lesser degree the secondary hematopoietic organs (the spleen, liver, and lymph nodes), and usually present with symptoms related to altered hematopoiesis. Three broad categories of myeloid neoplasia exist:

- *Acute myeloid leukemias*, in which an accumulation of immature myeloid forms (blasts) in the bone marrow suppresses normal hematopoiesis
- *Myelodysplastic syndromes*, in which defective maturation of myeloid progenitors gives rise to ineffective hematopoiesis, leading to cytopenias
- *Myeloproliferative disorders*, in which there is usually increased production of one or more types of blood cells

The pathogenesis of myeloid neoplasms is best understood in the context of normal hematopoiesis, which involves a hierarchy of hematopoietic stem cells, committed progenitors, and more differentiated elements (Fig. 13-1). Normal hematopoiesis is finely tuned by homeostatic feedback mechanisms involving cytokines and growth factors that modulate the production of red cells, white cells, and platelets in the marrow. These mechanisms are deranged in marrows involved by myeloid neoplasms, which "escape" from normal homeostatic controls and suppress the function of residual normal stem cells. The specific manifestations of the different myeloid neoplasms are influenced by

- *The position of the transformed cell within the hierarchy of progenitors* (i.e., a pluripotent hematopoietic stem cell versus a more committed progenitor)
- *The effect of the transforming events on differentiation*, which may be inhibited, skewed, or deranged by particular oncogenic mutations

Given that all myeloid neoplasms originate from transformed hematopoietic progenitors, it is not surprising that divisions between these neoplasms are sometimes blurred. Myeloid neoplasms, like other malignancies, tend to evolve over time to more aggressive forms of disease. In particular, both myelodysplastic syndromes and myeloproliferative disorders often "transform" to AML. In one of the most important myeloproliferative disorders, chronic myelogenous leukemia (CML), transformation to acute lymphoblastic leukemia is also seen, indicating that it originates from a transformed pluripotent hematopoietic stem cell.

Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is a tumor of hematopoietic progenitors caused by acquired oncogenic mutations that impede differentiation, leading to the accumulation of immature myeloid blasts in the marrow. The replacement of the marrow with blasts produces marrow failure and complications related to anemia, thrombocytopenia, and neutropenia. AML occurs at all ages, but the incidence rises throughout life, peaking after 60 years of age. There are about 13,000 new cases each year in the United States.

Classification. AML is quite heterogeneous, reflecting the complexities of myeloid cell differentiation. The current WHO classification subdivides AML into four categories (Table 13-10). The first includes forms of AML that are associated with particular genetic aberrations, which are important because they correlate with prognosis and guide therapy. Also included are categories of AML arising after a myelodysplastic disorder (MDS) or with MDS-like features, and therapy-related AML. AMLs in these two categories have distinct genetic features and respond poorly to