TABLE 132-1 WORLD HEALTH ORGANIZATION CLASSIFICATION OF ACUTE MYELOID LEUKEMIA (AML) AND RELATED NEOPLASMS[a]

AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1*[b]
AML with inv(16)(pl3.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*[b]
Acute promyelocytic leukemia with t(15;17)(q22;q12); *PML-RARA*[b]
AML with t(9;11)(p22;q23); *MLLT3-MLL*
AML with t(6;9)(p23;q34); *DEK-NUP214*
AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*
Provisional entity: AML with mutated NPM1
Provisional entity: AML with mutated CEBPA
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, not otherwise specified
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic and monocytic leukemia
Acute erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis
Myeloid leukemia associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasm

[a]From SH Swerdlow et al (eds): *World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues.* Lyon, IARC Press, 2008. [b]Diagnosis is AML regardless of blast count.

myelodysplasia-related changes based in part on medical history of an antecedent MDS or myelodysplastic/myeloproliferative neoplasm. The clinical features likely contribute to the prognosis of AML and have therefore been included in the classification.

Genetic Findings and Relevance to the WHO Classification The WHO classification uses clinical, morphologic, and cytogenetic and/or molecular criteria to identify subtypes of AML and forces the clinician to take the appropriate steps to correctly identify the entity and thus tailor treatment(s) accordingly. The WHO classification is indeed the first AML classification that incorporates genetic (chromosomal and molecular) information. In this classification, subtypes of AML are recognized based on the presence or absence of specific recurrent genetic abnormalities. For example, the diagnosis of *acute promyelocytic leukemia* (APL) is based on the presence of either the t(15;17)(q22;q12) cytogenetic rearrangement or the *PML-RARA* fusion product of the translocation. A similar approach is taken with regard to core binding factor (CBF) AML that is now designated based on the presence of t(8;21)(q22;q22), inv(16)(p13.1q22), or t(16;16)(p13.1;q22) or the respective fusion products *RUNX1-RUNX1T1* and *CBFB-MYH11*.

The WHO classification incorporates cytogenetics in the AML classification by recognizing a category of AML with recurrent genetic abnormalities and a category of AML with myelodysplasia-related changes (Table 132-1). The latter category is diagnosed not only by morphologic changes, but also in part by selected myelodysplasia-related cytogenetic abnormalities (e.g., complex karyotypes and unbalanced and balanced changes involving, among others, chromosomes 5, 7, and 11). Only one cytogenetic abnormality has been invariably associated with specific morphologic features: t(15;17)(q22;q12) with APL. Other chromosomal abnormalities have been associated primarily with one morphologic/immunophenotypic group, including inv(16)(p13.1q22) with AML with abnormal bone marrow eosinophils; t(8;21)(q22;q22) with slender Auer rods, expression of CD19, and increased normal eosinophils; and t(9;11)(p22;q23), and other translocations involving 11q23, with monocytic features. Recurring chromosomal abnormalities in AML may also be associated with specific clinical characteristics. More commonly associated with younger age are t(8;21) and t(15;17), and with older age, del(5q) and del(7q). Myeloid sarcomas (see below) are associated with t(8;21), and disseminated intravascular coagulation (DIC) is associated with t(15;17).

The WHO classification also incorporates molecular abnormalities by recognizing fusion genes that are products of recurrent cytogenetic aberrations or have been found mutated and may be involved in leukemogenesis. For instance, t(15;17) results in the fusion gene *PML-RARA* that encodes a chimeric protein, promyelocytic leukemia (Pml)–retinoic acid receptor α (Rarα), which is formed by the fusion of the retinoic acid receptor α (*RARA*) gene from chromosome 17 and the promyelocytic leukemia (*PML*) gene from chromosome 15. The *RARA* gene encodes a member of the nuclear hormone receptor family of transcription factors. After binding retinoic acid, *RARA* can promote expression of a variety of genes. The 15;17 translocation juxtaposes *PML* with *RARA* in a head-to-tail configuration that is under the transcriptional control of *PML*. Three different breakpoints in the *PML* gene lead to various fusion protein isoforms. The Pml-Rarα fusion protein tends to suppress gene transcription and blocks differentiation of the cells. Pharmacologic doses of the Rarα ligand, all-*trans*-retinoic acid (tretinoin), relieve the block and promote hematopoietic cell differentiation (see below). Similar examples of molecular subtypes of the disease included in the category of AML with recurrent genetic abnormalities are those characterized by the leukemogenic fusion genes *RUNX1-RUNX1T1*, *CBFB-MYH11*, *MLLT3-MLL*, and *DEK-NUP214*, resulting, respectively, from t(8;21), inv(16) or t(16;16), t(9;11), and t(6;9)(p23;q34).

Two new provisional entities defined by the presence of gene mutations, rather than microscopic chromosomal abnormalities, have been added to the category of AML with recurrent genetic abnormalities: *AML with mutated nucleophosmin (nucleolar phosphoprotein B23, numatrin)* (*NPM1*) and *AML with mutated CEBPA*. AML with fms-related tyrosine kinase 3 (*FLT3*) mutations is not considered a distinct entity, although determining the presence of such mutations is recommended by WHO in patients with cytogenetically normal AML (CN-AML) because the relatively frequent *FLT3*-internal tandem duplication (ITD) carries a negative prognostic significance and therefore is clinically relevant. *FLT3* encodes a tyrosine kinase receptor important in the development of myeloid and lymphoid lineages. Activating mutations of *FLT3* are present in ~30% of adult AML patients due to ITDs in the juxtamembrane domain or point mutations of the activating loop of the kinase (called tyrosine kinase domain mutations). Aberrant activation of the *FLT3*-encoded protein provides increased proliferation and antiapoptotic signals to the myeloid progenitor cell. *FLT3*-ITD, the more common of the *FLT3* mutations, occurs preferentially in patients with CN-AML. The importance of identifying *FLT3*-ITD at diagnosis relates to the fact that not only is it a useful prognosticator but it also may predict response to specific treatment such as the tyrosine kinase inhibitors that are in clinical investigation.

PROGNOSTIC FACTORS

Several factors have been demonstrated to predict outcome of AML patients treated with chemotherapy, and they can be used for risk stratification and treatment guidance.

Chromosome findings at diagnosis are currently the most important independent prognostic factors. Several studies have categorized patients as having favorable, intermediate, or poor cytogenetic risk based on the presence of structural and/or numerical aberrations. Patients with t(15;17) have a very good prognosis (~85% cured), and those with t(8;21) and inv(16) have a good prognosis (~55% cured), whereas those with no cytogenetic abnormality have an intermediate outcome risk (~40% cured). Patients with a complex karyotype, t(6;9), inv(3), or –7 have a very poor prognosis. Another cytogenetic subgroup, the monosomal karyotype, has been suggested to adversely