SPECIAL ARTICLE

World Health Organization Classification of Neoplastic Diseases of the Hematopoietic and Lymphoid Tissues: Report of the Clinical Advisory Committee Meeting—Airlie House, Virginia, November 1997

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Purpose: **The European Association of Hematopathologists and the Society for Hematopathology have developed a new World Health Organization (WHO) classification of hematologic malignancies, including lymphoid, myeloid, histiocytic, and mast cell neoplasms.**

Design: **Ten committees of pathologists developed lists and definitions of disease entities. A clinical advisory committee (CAC) of international hematologists and oncologists was formed to ensure that the classification would be useful to clinicians. The CAC met in November 1997 to discuss clinical issues related to the classification.**

Results: **The WHO uses the Revised European-American Lymphoma (REAL) classification, published in 1994 by the International Lymphoma Study Group, to categorize lymphoid neoplasms. The REAL classification is based on the principle that a classification is a list of "real" disease entities, which are defined by a combination of morphology, immunophenotype, genetic features, and clinical features. The relative importance of each of these features varies among diseases, and there is no one gold standard. The WHO classification applies the principles of the REAL classification to myeloid and histiocytic neoplasms. The classification of myeloid neoplasms recognizes distinct entities defined by a combination of morphology and cytogenetic abnormalities. At the CAC meeting, which was organized around a series of clinical questions, participants reached a consensus on most of the questions posed. They concluded that clinical groupings of lymphoid neoplasms were neither necessary nor desirable. Patient treatment is determined by the specific type of lymphoma, with the addition of grade within the tumor type, if applicable, and clinical prognostic factors, such as the International Prognostic Index.**

Conclusion: **The WHO classification has produced a new and exciting degree of cooperation and communication between oncologists and pathologists from around the world, which should facilitate progress in the understanding and treatment of hematologic malignancies.**

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THE SOCIETY FOR Hematopathology and the European Association of Hematopathologists jointly developed a classification of hematologic neoplasms for the World Health Organization (WHO). A steering committee composed of members of both societies was formed, and 10 committees were assigned the task of arriving at a consensus list of myeloid, lymphoid, and histiocytic neoplasms, with descriptions and criteria for diagnosis. A new classification for lymphoid neoplasms was recently proposed,[1] and the goals of the WHO project were to update and revise that classification, with input from additional experts in order to broaden the consensus, and to extend the principles of disease definition and consensus building to the myeloid and histiocytic neoplasms. More than 50 pathologists from around the world were involved in the project, which began in 1995. Proponents of all major lymphoma and leukemia classifications agreed that if a reasonable consensus emerged from this effort, they would accept the WHO classification of hematologic malignancies as the standard.

The proposed WHO classification of hematologic malignancies stratifies neoplasms primarily according to their lineage: myeloid neoplasms (Table 1), lymphoid neoplasms (Tables 2 and 3), mast cell disorders (Table 4), and histiocytic neoplasms (Table 5). Variants and subtypes of selected neoplasms are listed in Tables 6 through 15. Within each category, distinct diseases are defined according to a

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Table 1. Proposed WHO Classification of Myeloid Neoplasms

Myeloproliferative diseases
Chronic myelogenous leukemia, Philadelphia chromosome positive (t(9;22)(qq34;q11), *BCR/ABL*)
Chronic neutrophilic leukemia
Chronic eosinophilic leukemia/hypereosinophilic syndrome
Chronic idiopathic myelofibrosis
Polycythemia vera
Essential thrombocythemia
Myeloproliferative disease, unclassifiable
Myelodysplastic/myeloproliferative diseases
Chronic myelomonocytic leukemia
Atypical chronic myelogenous leukemia
Juvenile myelomonocytic leukemia
Myelodysplastic syndromes
Refractory anemia
With ringed sideroblasts
Without ringed sideroblasts
Refractory cytopenia (myelodysplastic syndrome) with multilineage dysplasia
Refractory anemia (myelodysplastic syndrome) with excess blasts
5q− syndrome
Myelodysplastic syndrome, unclassifiable
Acute myeloid leukemias*
AMLs with recurrent cytogenetic translocations
AML with t(8;21)(q22;q22), AML1(CBF-alpha)/ETO
Acute promyelocytic leukemia (AML with t(15;17)(q22;q11-12) and variants, PML/RAR-alpha)
AML with abnormal bone marrow eosinophils (inv(16)(p13q22) or t(16;16)(p13;q11), CBFβ/MYH11X)
AML with 11q23 (MLL) abnormalities
AML with multilineage dysplasia
With prior myelodysplastic syndrome
Without prior myelodysplastic syndrome
AML and myelodysplastic syndromes, therapy-related
Alkylating agent–related
Epipodophyllotoxin-related (some may be lymphoid)
Other types
AML not otherwise categorized
AML minimally differentiated
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monocytic leukemia
Acute erythroid leukemia
Acute megakaryocytic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Acute biphenotypic leukemias

NOTE: Only major disease categories are listed; subtypes and variants will be discussed in detail in the WHO book.[2]

Abbreviation: AML, acute myeloid leukemia.

*Acute lymphoid leukemias are included under lymphoid neoplasms and in Table 6.

combination of morphology, immunophenotype, genetic features, and clinical syndromes. The relative importance of each criterion differs among the neoplasms, and there is no one gold standard for classification of all hematologic malignancies. The goal was to define disease entities that could be recognized by pathologists and that have clinical relevance.

To ensure that the proposed classification would be of maximal use to oncologists, the steering committee invited expert hematologists and oncologists to form a clinical advisory committee (CAC), with American and European co-chairs. The charge to the CAC was to review the proposed classification and advise the pathologists on its clinical utility. More than 40 hematologists and oncologists from around the world agreed to participate. The proposed classification was circulated, and all participants were invited to submit topics and questions for discussion. A meeting was held in November 1997, at Airlie House, VA, involving the CAC, all pathologists involved in the WHO committees, and the executive committees of the two hematopathology societies.

The meeting was organized around a series of questions developed from those submitted by CAC members and posed by the pathologists. Only controversial issues were discussed; diseases were accepted as previously defined if there were no new questions or data. Only lymphoid and myeloid neoplasms were discussed at the meeting; histiocytic and mast cell tumors were not considered. Participants were invited to present data relevant to each question, and open discussion followed. At the end of each session, the clinicians were asked to arrive at a consensus regarding each question (as well as other issues raised at the meeting); if necessary, a show of hands was taken as a vote. After the meeting, participants were polled to resolve residual questions; several additional meetings of the pathology steering committee and the CAC co-chairs were held for the same purpose. The final classification will be published under the auspices of the WHO.[2]

MYELOID NEOPLASMS

Despite advances in the understanding of genetic factors in the biology of the myeloid neoplasms, particularly the acute leukemias, the classification of these disorders has not been recently updated. Thus, discussion of these disorders generated considerable controversy. At several subsequent meetings of pathologists and the clinical co-chairs, a consensus on the classification emerged. The following summary includes issues raised at the CAC meeting and resolutions achieved subsequently.

In the French-American-British (FAB) classification, three main categories of myeloid neoplasms are recognized: acute myeloid leukemias, myelodysplastic syndromes, and myelo-

Table 2. Proposed WHO Classification of Lymphoid Neoplasms

B-Cell neoplasms
Precursor B-cell neoplasm
Precursor B-lymphoblastic leukemia/lymphoma (precursor B-cell acute lymphoblastic leukemia)
Mature (peripheral) B-cell neoplasms*
B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
B-cell prolymphocytic leukemia
Lymphoplasmacytic lymphoma
Splenic marginal zone B-cell lymphoma (+/− villous lymphocytes)
Hairy cell leukemia
Plasma cell myeloma/plasmacytoma
Extranodal marginal zone B-cell lymphoma of MALT type
Nodal marginal zone B-cell lymphoma (+/− monocytoid B cells)
Follicular lymphoma
Mantle-cell lymphoma
Diffuse large B-cell lymphoma
Mediastinal large B-cell lymphoma
Primary effusion lymphoma
Burkitt's lymphoma/Burkitt cell leukemia
T-cell and NK-cell neoplasms
Precursor T-cell neoplasm
Precursor T-lymphoblastic lymphoma/leukemia (precursor T-cell acute lymphoblastic leukemia)
Mature (peripheral) T-cell neoplasms*
T-cell prolymphocytic leukemia
T-cell granular lymphocytic leukemia
Aggressive NK-cell leukemia
Adult T-cell lymphoma/leukemia (HTLV1+)
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-type T-cell lymphoma
Hepatosplenic gamma-delta T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides/Sezary syndrome
Anaplastic large-cell lymphoma, T/null cell, primary cutaneous type
Peripheral T-cell lymphoma, not otherwise characterized
Angioimmunoblastic T-cell lymphoma
Anaplastic large-cell lymphoma, T/null cell, primary systemic type
Hodgkin's lymphoma (Hodgkin's disease)
Nodular lymphocyte-predominant Hodgkin's lymphoma
Classical Hodgkin's lymphoma
Nodular sclerosis Hodgkin's lymphoma (grades 1 and 2)
Lymphocyte-rich classical Hodgkin's lymphoma
Mixed cellularity Hodgkin's lymphoma
Lymphocyte depletion Hodgkin's lymphoma

NOTE: Only major categories are included. Subtypes and variants will be discussed in the WHO book[2] and are listed in Tables 7 through 16. Common entities are shown in boldface type.

Abbreviations: HTLV1+, human T-cell leukemia virus; MALT, mucosa-associated lymphoid tissue; NK, natural killer.

*B- and T-/NK-cell neoplasms are grouped according to major clinical presentations (predominantly disseminated/leukemic, primary extranodal, predominantly nodal).

Table 3. Categories of Posttransplant Lymphoproliferative Disorders

Early lesions
Reactive plasmacytic hyperplasia
Infectious mononucleosis-like
PTLD, polymorphic
Polyclonal (rare)
Monoclonal
PTLD, monomorphic (classify according to lymphoma classification)
B-cell lymphomas
Diffuse large B-cell lymphoma (immunoblastic, centroblastic, anaplastic)
Burkitt's/Burkitt-like lymphoma
Plasma cell myeloma
T-cell lymphomas
Peripheral T-cell lymphoma, not otherwise categorized
Other types (hepatosplenic, gamma-delta, T/NK)
Other types, rare
Hodgkin's disease-like lesions (associated with methotrexate therapy)
Plasmacytoma-like lesions

proliferative disorders.[3] The blast count, lineage commitment, and level of differentiation of the neoplastic cells are the major determinants of the categories recognized, using morphologic, cytochemical, and immunophenotypic features. Recently, genetic features (cytogenetic and molecular genetic), as well as other features, such as prior therapy and a history of myelodysplasia, have been shown to have a significant impact on the clinical behavior of these disorders, and these features do not always correlate perfectly with the FAB categories. Thus, a major focus of debate was how to integrate genetic and clinical features with morphology, cytochemistry, and immunophenotype into a classification that could be used by pathologists and have clinical relevance. A key issue, as with the lymphoid neoplasms, was to discriminate between disease entities and prognostic factors. Some genetic abnormalities seem to define distinct diseases, whereas others are prognostic factors within a given disease. Also debated was whether all diseases fit into one of the three major categories or whether additional broad categories are needed.

After discussion, it seemed that a paradigm similar to that adopted for the Revised European-American Lymphoma (REAL) classification could at least tentatively apply to the myeloid disorders; namely, a combination of morphology, immunophenotype, genetic features, and clinical features could be used to define distinct disease entities. The technology of genetic analysis is evolving rapidly, and it is likely that advances in this field will necessitate revisions to

Table 4. Mast Cell Diseases

Cutaneous mastocytosis
Systemic mast cell disease (+/− skin involvement)
Systemic mast cell disease with associated hematologic disorder (+/− skin involvement)
Mast cell leukemia/sarcoma

Table 5. Histiocytic and Dendritic Cell Neoplasms

Macrophage/histiocytic neoplasm
Histiocytic sarcoma
Dendritic Cell neoplasms
Langerhans cell histiocytosis
Langerhans cell sarcoma
Interdigitating dendritic cell sarcoma/tumor
Follicular dendritic cell sarcoma/tumor
Dendritic cell sarcoma, not otherwise specified

any current classification in the near future. The pathologists proposed four major groups of myeloid diseases: myeloproliferative diseases (MPDs), myelodysplastic/myeloproliferative diseases (MD/MPDs), myelodysplastic syndromes (MDSs), and acute myeloid leukemias (AMLs). Within the category of AML, four main groups are recognized: (1) AML with recurrent cytogenetic translocations; (2) AML with myelodysplasia-related features; (3) therapy-related AML and MDS; and (4) AML not otherwise specified.

Myeloproliferative Diseases

MPDs are clonal stem-cell disorders characterized by ''effective'' hematopoiesis that results in elevated peripheral-blood levels of one or more cell lines and hepatosplenomegaly; the marrow is hypercellular with maturation and without dysplasia. Among the MPDs, the prototype is Philadelphia chromosome (Ph1)–positive (*BCR/ABL*$^+$) chronic myelogenous leukemia (CML). The other accepted entities are polycythemia vera, idiopathic myelofibrosis, and essential thrombocythemia. Controversies within this group include the definitions and classification of juvenile myelomonocytic leukemia (JMML; also known as juvenile chronic myeloid leukemia and juvenile chronic myelomonocytic leukemia), chronic myelomonocytic leukemia (CMML), and atypical CML.

Should JMML be a separate category? Should it be classified as an MDS or an MPD? The CAC accepted the conclusions of the International Study Group for Pediatric MDS that JMML is a separate disorder, distinct from adult chronic myeloid or myelomonocytic leukemia. CAC members proposed that the term JMML be adopted. They favored including it in the MPDs; however, the pathologists recommended that a separate category be formed to include JMML and other disorders that combine features of myeloproliferative and myelodysplastic syndromes.

Table 6. Acute Lymphoid Leukemias

Precursor B-cell acute lymphoblastic leukemia (cytogenetic subgroups)
t(9;22)(a34;q11); *BCR/ABL*
t(v;11q23); *MLL* rearranged
t(1;19)(q23;p13) *E2A/PBX1*
t(12;21)(p12;q22) *ETV/CBF*-alpha
Precursor T-cell acute lymphoblastic leukemia
Burkitt-cell leukemia

Table 7. B-Cell Neoplasms, Predominantly Disseminated/Leukemic Types, Variants

B-cell CLL/SLL
Variant: with monoclonal gammopathy/plasmacytoid differentiation
Hairy cell leukemia
Variant: hairy cell leukemia variant

Should CMML be divided into MDS and MPD types? CMML has long been recognized as a disorder that has features of both myelodysplastic and myeloproliferative syndromes. Nearly half the patients present with low or normal neutrophil counts, multilineage marrow dysplasia, no organomegaly, and bone marrow morphology that resembles refractory anemia with excess blasts (RAEB) but with monocytosis. Other patients have marked neutrophilia, monocytosis, and splenomegaly. It has been debated whether this is really two diseases—one an MDS and the other an MPD. However, studies to date have shown no differences in cytogenetic abnormalities, oncogene mutations, in vitro colony growth patterns, or clinical outcome between the two types of CMML. It was the consensus at the meeting that CMML is one disease. The CAC concluded that CMML fits better in the MPD than in the MDS category, but after subsequent discussions, the pathologists recommended that it be included in a separate category, along with JMML, of disorders with both myeloproliferative and myelodysplastic features.

What should the nomenclature and category be for atypical CML (aCML)? Atypical CML was first recognized as a disease involving predominantly the neutrophil series and lacking Ph1 or the *BCR/ABL* translocation. It has dysplastic as well as proliferative features and often occurs with multilineage dysplasia. The prognosis is significantly worse than that for Ph1$^+$ CML. It is clear that it is clinically, genetically, and morphologically distinct from Ph1$^+$ CML; therefore, the term aCML is suboptimal, implying both a

Table 8. Follicular and Mantle-Cell Lymphomas: Grading and Variants

Follicular lymphoma
Grade 1, 0-5 centroblasts/hpf
Grade 2, 6-15 centroblasts/hpf
Grade 3, > 15 centroblasts/hpf
3a, > 15 centroblasts, but centrocytes are still present
3b, Centroblasts form solid sheets with no residual centrocytes
Variants
Cutaneous follicle center lymphoma
Diffuse follicle center lymphoma
Grade 1, 0-5 CB/hpf
Grade 2, 6-15 CB/hpf
Mantle-cell lymphoma
Variant: blastoid

Table 9. DLBCL, Morphologic Variants and Subtypes

Morphologic variants
Centroblastic
Immunoblastic
T-cell/histiocyte-rich
Lymphomatoid granulomatosis type
Anaplastic large B-cell
Plasmablastic
Subtypes
Mediastinal (thymic) large B-cell lymphoma
Primary effusion lymphoma
Intravascular large B-cell lymphoma

relationship to $Ph1^+$ CML and a chronic process. The CAC was unable to agree on another name, and thought the term aCML could be retained, provided the disease was clearly defined so as to prevent confusion. The pathologists recommended placing aCML with JMML and CMML in a category of MD/MPD.

Should there be a separate category for cases that are neither MDS nor MPD? For reasons mentioned above, the pathologists recommended a fourth category of myeloid neoplasms to contain those cases that are inherently proliferative but show dysplastic features, such as JMML, CMML, and aCML. It was the opinion of the clinicians that such a category was not desirable and that these diseases could be placed in the MPD category. The pathologists contended that these disorders have many common features, including abnormalities of both the granulocytic and monocytic lines and a relatively aggressive course, that distinguish them from the MDS and MPD categories and argued for placing them together.

MPDs: Summary.

1. Should JMML be a separate category? YES
2. Should CMML be divided into MDS and MPD types? NO
3. What should we call aCML? aCML
4. Should there be a separate category for cases that are neither MDS nor MPD? NO CONSENSUS
   - Pathologists proposed a category of MDS/MPD to include JMML, CMML, and aCML.

Acute Myeloid Leukemia and Myelodysplastic Syndrome

What blast count should define AML? According to the FAB standard, AML is defined by the presence of 30% blasts. However, recent studies have indicated that patients with 20% to 30% blasts (classified as RAEB in transformation) have a prognosis similar to that of patients with more than 30% blasts. Thus, there was a consensus that the blast count for the diagnosis of AML should be 20% and the RAEB in transformation category should be dropped.

Table 10. Burkitt's Lymphoma, Morphologic Variants and Subtypes

Morphologic variants
Burkitt-like
With plasmacytoid differentiation (AIDS-associated)
Subtypes, clinical and genetic
Endemic
Sporadic
Immunodeficiency-associated

Table 11. Plasma Cell Disorders: Subtypes and Variants

Monoclonal gammopathy of undetermined significance
Plasma cell myeloma variants
Indolent myeloma
Smoldering myeloma
Osteosclerotic myeloma (POEMS syndrome)
Plasma cell leukemia
Nonsecretory myeloma
Plasmacytoma variants
Solitary plasmacytoma of bone
Extramedullary plasmacytoma

Abbreviation: POEMS, polyneuropathy, organomegaly, endocrinopathy, M-component, skin changes.

Should cytogenetic/molecular categories of AML be recognized as distinct diseases? Several specific cytogenetic abnormalities in AML are associated with characteristic morphology and have distinctive clinical features. With the exception of promyelocytic leukemia/M3 with t(15;17), these genetic abnormalities do not correlate precisely with FAB categories. The consensus of the CAC was that these categories should be recognized as distinct entities within the classification. After discussion, the pathologists agreed that it would be possible to develop morphologic criteria for these categories that would permit them to be recognized, or at least suspected, by pathologists, who should then suggest confirmation by genetic analysis. The following specific categories will be defined: (1) AML with t(8;21)(q22;q22), AML1(*CBF*-alpha)/*ETO*; (2) acute promyelocytic leukemia (AML with t(15;17)(q22;q11-12) and variants, *PML/RAR*-alpha); (3) AML with abnormal bone marrow eosinophils (inv(16)(p13q22) or t(16;16)(p13;q22), *CBF*-beta/*MYH11*); and (4) AML with 11q23 (*MLL*) abnormalities.

Table 12. Immunosecretory Disorders (clinical manifestations of diverse lymphoid neoplasms)

Clinical Syndrome	Underlying Neoplasm
Waldenström's macroglobulinemia	Lymphoplastmacytic lymphoma
Heavy-chain diseases	
Gamma HCD	Lymphoplasmacytic lymphoma
Alpha HCD	Extranodal marginal zone lymphoma (immunoproliferative small intestinal disorder)
Mu HCD	B-cell CLL
Immunoglobulin deposition diseases	
Systemic light-chain disease	Plasma cell myeloma, monoclonal gammopathy
Primary amyloidosis	Plasma cell myeloma, monoclonal gammopathy

Abbreviation: HCD, heavy-chain disease.

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