

The World Health Organization Classification of Hematological Malignancies Report of the Clinical Advisory Committee Meeting, Airlie House, Virginia, November 1997

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Since 1995, the European Association of Pathologists and the Society for Hematopathology have been developing a new World Health Organization (WHO) classification of hematologic malignancies. The classification includes lymphoid, myeloid, histiocytic, and mast cell neoplasms.

The WHO project involves 10 committees of pathologists, who have developed lists and definitions of disease entities. A Clinical Advisory Committee of international hematologists and oncologists was formed to ensure that the classification will be useful to clinicians. A meeting was held in November 1997 to discuss clinical issues related to the classification. The WHO has adopted the Revised European-American Classification of Lymphoid Neoplasms, published in 1994 by the International Lymphoma Study Group, as the classification of lymphoid neoplasms. This approach to 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 has applied the principles of the Revised European-American Classification of Lym-

phoid Neoplasms to myeloid and histiocytic neoplasms. The classification of myeloid neoplasms recognizes distinct entities defined by a combination of morphology and cytogenetic abnormalities.

The Clinical Advisory Committee meeting, which was organized around a series of clinical questions, was able to reach a consensus on most of the questions posed. The questions and the consensus are discussed in detail in this article. Among other things, the Clinical Advisory Committee concluded that clinical grouping of lymphoid neoplasms was 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.

The experience of developing the WHO classification has produced a new and exciting degree of cooperation and communication between oncologists and pathologists from around the world. This should facilitate progress in the understanding and treatment of hematologic malignancies.

KEY WORDS: Classification, Histiocytic, Leukemia, Lymphoma, Mast cell, Myeloid.

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The Society for Hematopathology and the European Association of Hematopathologists have undertaken as a joint project the development of a classification of hematologic neoplasms for the World Health Organization (WHO). A steering committee composed of members of both societies has been formed, and 10 committees have been 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 are to update and revise that classification, with input from additional experts 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 have been involved in the project since 1995. Proponents of all major lymphoma and leukemia classifications have agreed that if a reasonable consensus emerges from this effort, they will accept the WHO as the standard classification of hematologic malignancies.

The proposed WHO classification of hematologic malignancies stratifies these neoplasms primarily according to lineage: myeloid neoplasms, lymphoid neoplasms, mast cell disorders, and histiocytic neoplasms (Tables 1–5). Within each category, distinct diseases are defined according to a combination of morphology, immunophenotype, genetic features, and clinical syndromes. The relative importance of each of these criteria differs among the neoplasms, and there is no one gold standard for classification of all hematologic malignancies. The goal is to define disease entities that can be recognized by pathologists and that have clinical relevance.

To ensure that the proposed classification will be of maximum 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 committee 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, Virginia, to which the CAC and all pathologists involved in the WHO committees, as well as the Executive Committees of the two hematopathology societies, were invited.

The meeting was organized around a series of questions, developed from those submitted by CAC members as well as those posed by the pathologists. Only issues that were controversial were discussed; diseases for which there were no new questions or data were accepted as previously defined. Only lymphoid and myeloid neoplasms were discussed at this 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 present were asked to arrive at a consensus regarding each question (as well as on other issues raised at the meeting); when necessary, a

TABLE 1. Proposed WHO Classification of Myeloid Neoplasms

Myeloproliferative Diseases (MPD)
Chronic myelogenous leukemia, Philadelphia chromosome (Ph1) [t(9;22)(q34;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 (CMML)
Atypical chronic myelogenous leukemia (aCML)
Juvenile myelomonocytic leukemia (JMML)
Myelodysplastic Syndromes (MDS)
Refractory anemia (RA)
with ringed sideroblasts (RARS)
without ringed sideroblasts
Refractory cytopenia (myelodysplastic syndrome) with multilineage dysplasia (RCMD)
Refractory anemia (myelodysplastic syndrome) with excess blasts (RAEB)
5q- syndrome
Myelodysplastic syndrome, unclassifiable
Acute Myeloid Leukemias (AML) ^a
Acute myeloid leukemias with recurrent cytogenetic translocations
AML with t(8;21)(q22;q22), AML1(CBF α)/ETO
Acute promyelocytic leukemia (AML with t(15;17)(q22;q11-12) and variants, PML/RAR α)
AML with abnormal bone marrow eosinophils (inv(16)(p13q22) or t(16;16)(p13;q11), CBF β /MYH11X)
AML with 11q23 (MLL) abnormalities
Acute myeloid leukemia with multilineage dysplasia
with prior myelodysplastic syndrome
without prior myelodysplastic syndrome
Acute myeloid leukemia and myelodysplastic syndrome, therapy related
Alkylating agent related
Epipodophyllotoxin related (some may be lymphoid)
Other types
Acute myeloid leukemia (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 Biphentotypic Leukemias

Only major disease categories are listed; subtypes and variants will be discussed in detail in the text.

^a Acute lymphoid leukemias are included under lymphoid neoplasms and in Table 7.

show of hands was taken as a vote. Following the meeting, a poll of the participants, as well as several additional meetings of the pathology Steering Committee and the co-chairs of the CAC, was held to resolve residual questions. The final classification will be published under the auspices of the WHO (2).

MYELOID NEOPLASMS

Although there have been many advances in the understanding of genetic factors in the biology of the myeloid neoplasms, particularly the acute leu-

TABLE 2. Proposed WHO Classification of Lymphoid Neoplasms

B-Cell Neoplasms
Precursor B-cell neoplasm
<u>Precursor B-lymphoblastic leukemia/lymphoma (precursor B-cell acute lymphoblastic leukemia)</u>
Mature (peripheral) B-cell neoplasms ^a
B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
B-cell prolymphocytic leukemia
Lymphoplasmacytic lymphoma
Splenic marginal zone B-cell lymphoma (\pm villous lymphocytes)
Hairy cell leukemia
<u>Plasma cell myeloma</u> /plasmacytoma
<u>Extranodal marginal zone B-cell lymphoma of MALT type</u>
Nodal marginal zone B-cell lymphoma (\pm monocytoid B cells)
<u>Follicular lymphoma</u>
<u>Mantle cell lymphoma</u>
<u>Diffuse large B-cell lymphoma</u>
Mediastinal large B-cell lymphoma
Primary effusion lymphoma
<u>Burkitt lymphoma/Burkitt cell leukemia</u>
T and NK-Cell Neoplasms
Precursor T-cell neoplasm
<u>Precursor T-lymphoblastic lymphoma/leukemia (precursor T-cell acute lymphoblastic leukemia)</u>
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
<u>Mycosis fungoides/Sezary syndrome</u>
Anaplastic large cell lymphoma, T/null cell, primary cutaneous type
<u>Peripheral T-cell lymphoma, not otherwise characterized</u>
<u>Angioimmunoblastic T-cell lymphoma</u>
Anaplastic large cell lymphoma, T/null cell, primary systemic type
Hodgkin lymphoma (Hodgkin disease)
Nodular lymphocyte predominance Hodgkin lymphoma
Classical Hodgkin lymphoma
<u>Nodular sclerosis Hodgkin lymphoma (Grades 1 and 2)</u>
Lymphocyte-rich classical Hodgkin lymphoma
<u>Mixed cellularity Hodgkin lymphoma</u>
Lymphocyte depletion Hodgkin lymphoma

Only major categories are included. Subtypes and variants will be discussed in the WHO book (2) and in Tables 7–16. More common entities are underlined.

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

kemias, the classification of these disorders has not been recently updated. Thus, the discussion of these disorders generated considerable controversy, and several subsequent meetings of pathologists and the clinical co-chairs occurred, during which a consensus on the classification emerged. The following summary includes both 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 myeloproliferative disorders (3). The blast count, lineage commitment, and level of differentiation of the neoplastic cells are the major determinants of the categories recog-

TABLE 3. Categories of Posttransplant Lymphoproliferative Disorders (PTLD)

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/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 disease-like lesions (associated with methotrexate therapy)
Plasmacytoma-like lesions

TABLE 4. Mast Cell Diseases

Cutaneous mastocytosis
Systemic mast cell disease (\pm skin involvement)
Systemic mast cell disease with associated hematologic disorder (\pm 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

nized, using morphologic, cytochemical, and immunophenotypic features. Recently, genetic features (cytogenetic and molecular genetic) as well as other features, such as previous 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 can be used by pathologists and that will 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. Another issue debated was whether all diseases fit into one of the three major categories or additional broad categories are needed.

After discussion, it seemed that a paradigm similar to that adopted for the Revised European-American Classification of Lymphoid Neoplasms (REAL) can at least tentatively apply to the myeloid disorders; namely, that a combination of morphology, immuno-

phenotype, genetic features, and clinical features is used to define distinct disease entities. The technology of genetic analysis is moving rapidly, and it is likely that advances in this field will necessitate revisions to any current classification in the near future. The pathologists proposed four major groups of myeloid diseases: myeloproliferative diseases (MPD), myelodysplastic/myeloproliferative diseases (MD/MPD), myelodysplastic syndromes (MDS), and acute myeloid leukemias (AML). 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 (NOS).

Myeloproliferative Diseases

MPD are clonal stem cell disorders that are characterized by “effective” hematopoiesis, resulting in elevated peripheral blood levels of one or more cell lines and hepatosplenomegaly; there is marrow hypercellularity with maturation and without dysplasia. Among the MPD, the prototype is Philadelphia chromosome (Ph1)+ [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 (also known as juvenile chronic myeloid leukemia and juvenile chronic myelomonocytic leukemia), chronic myelomonocytic leukemia, and atypical CML (aCML).

Should juvenile myelomonocytic leukemia be a separate category? Should it be classified as MDS or MPD? The CAC accepted the conclusions of the international study group for pediatric MDS that juvenile myelomonocytic leukemia is a separate disorder, distinct from adult chronic myeloid or myelomonocytic leukemias. It has been proposed that the name *juvenile myelomonocytic leukemia (JMML)* be adopted. The committee favored including it in the myeloproliferative disorders; however, the pathologists recommended that a separate category be formed to include this and other disorders that combine features of myeloproliferative and myelodysplastic syndromes.

Should chronic myelomonocytic leukemia (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 of 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 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 of the meeting that this is one disease. The committee concluded that it 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, with JMML, of disorders with both myeloproliferative and myelodysplastic features.

What should be the nomenclature and category for aCML? This disease was first recognized as a disease involving predominantly the neutrophil series, that lacked Ph1 or BCR/ABL translocation, which has dysplastic as well as proliferative features, often with multilineage dysplasia. The prognosis is significantly worse than that of Ph1+ CML. It is clear that it is clinically, genetically, and morphologically distinct from Ph1+ CML, and the name is therefore suboptimal, implying both a relationship to Ph1+ CML and a chronic process. The committee was unable to agree on another name and believed that the term *aCML* could be retained, provided that a clear definition of the disease was provided to prevent confusion. The pathologists recommended placing this disease with JMML and CMML in a category of myelodysplastic/myeloproliferative diseases.

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, including JMML, CMML, and aCML. It was the opinion of the clinicians present that such a category was not desirable and that these diseases could be placed in the MPD category. However, the pathologists contended that these disorders have many features in common, including abnormalities of both granulocytic and monocytic lines and a relatively aggressive course, that distinguish them from both the MDS and MPD categories and argued for placing them together.

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 “atypical CML”? Atypical CML
4. Should there be a separate category for cases that are neither MDS nor MPD? No consensus
 - Pathologists propose a category of MDS/MPD, to include JMML, CMML, and aCML.

Acute Myeloid Leukemia and Myelodysplastic Syndromes

What blast count should define AML? The FAB standard has been 30% blasts. However, recent studies have indicated that patients with 20 to 30% blasts (classified as RAEB in transformation [RAEB-T]) 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 category of RAEB-T should be dropped.

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, which would permit them to be recognized, or at least suspected, by pathologists, who should then suggest confirmation by genetic analysis. The specific categories that will be defined are

1. AML with t(8;21)(q22;q22), AML1(CBF α)/ETO
2. Acute promyelocytic leukemia (AML with t[15;17][q22;q11-12] and variants, PML/RAR α)
3. AML with abnormal bone marrow eosinophils (inv [16][p13q22] or t[16;16][p13;q22], CBF β /MYH11)
4. AML with 11q23 (MLL) abnormalities

The specific morphologic features of these disorders will be described in the classification (2), and these entities will be excluded from the FAB categories used for cases that lack these abnormalities. In addition, cases with these specific cytogenetic abnormalities with low blast counts, which might in the past have been diagnosed as MDS, will now be classified as AML.

Should multilineage dysplasia, prior MDS, and/or prior therapy be included in classification of AML? Severe multilineage dysplasia, defined as the presence of dysplastic features in the cells of two or more lines, has been shown to be associated with poor outcome in AML. Similarly, AML arising in patients with a history of MDS also have a poor prognosis. Therapy-related leukemias secondary to alkylating agent therapy are clearly different from many *de novo* acute leukemias; they are associated with characteristic cytogenetic abnormalities (3q-, -5, 5q-, -7, 7q-, +8, +9, 11q-, 12p-, -18, -19, 20q-, +21, t[1;7], t[2;11], complex karyotypes) and a worse prognosis and

often show multilineage dysplasia or are preceded by a hypoproliferative state with multilineage dysplasia, resembling MDS. Similar cytogenetic abnormalities are often seen in MDS not associated with prior therapy, as well as in *de novo* acute leukemias, particularly in older adults. It has been suggested that all of these disorders reflect similar genetic damage, which may be either environmental or iatrogenic. There was a consensus that the presence of multilineage dysplasia at the time of the diagnosis of acute leukemia, a history of myelodysplasia, and prior alkylating agent therapy all were adverse prognostic factors, which may reflect a common pathogenesis. The committee concluded that multilineage dysplasia, a history of MDS, and a history of alkylating agent therapy should be included in the classification of AML.

The specific cytogenetic abnormalities common to MDS, alkylating agent-related AML, and poor-prognosis AML (3q-, -5, 5q-, -7, 7q-, +8, +9, 11q-, 12p-, -18, -9, 20q-, +21, t[1;7], t[2;11], complex karyotypes) likely reflect a common pathogenesis of these lesions, distinct from that of other *de novo* AML. However, there was no consensus on the role of these abnormalities in defining disease entities within the classification. Our understanding of this issue likely will improve in the near future, necessitating a change in the major groupings. For the present, cytogenetic abnormalities indicative of poor prognosis should be recognized as prognostic factors within each category of AML.

Therapy with topoisomerase II inhibitors (epidophyllotoxins and adriamycin) is also associated with secondary leukemias, which are often myeloid but may be lymphoid. These typically show cytogenetic abnormalities associated with *de novo* AML—most commonly translocations involving 11q23 (MLL) but also occasionally t(8;21), inv (16), or t(15;17). These cases should also be recognized in the classification as distinct from alkylating agent-related secondary leukemias.

Should refractory cytopenia with multilineage dysplasia be a separate category? Myelodysplastic syndromes are clonal stem cell disorders characterized by ineffective hematopoiesis, resulting clinically in peripheral blood cytopenias; the marrow is variably hypercellular, and patients show poor responses to chemotherapy, with an increased risk of progression to acute leukemia. The terms *refractory anemia* and *refractory anemia with ring sideroblasts* were defined in the FAB classification as having dysplasia largely restricted to the erythroid line. Recent studies have shown that patients who have MDS with less than 5% blasts but with significant dysplasia involving

granulocytic and megakaryocytic lines have a worse prognosis and are more likely to die of marrow failure or progress to acute leukemia (similar to RAEB) than those lacking these features. Thus, the committee agreed that a separate category is needed for these cases. Multilineage dysplasia is defined as the presence of dysplastic features in the cells of two or more lines. Refractory anemia (with or without ring sideroblasts) will continue to be defined as a disorder involving the erythroid line only. MDS will exclude cases of low blast-count leukemias that show one of the AML-type cytogenetic abnormalities—t(8;21), inv(16), or t(15;17). Because of the distinctive morphologic and clinical features of the 5q- syndrome, it was agreed by the pathologists that this should be a separate category within MDS.

Summary

1. What blast count should define AML? 20%
 - Eliminate RAEB-T
2. Should cytogenetic/molecular categories be recognized as distinct diseases? Yes
 - t(8;21)(q22;q22), AML1(CBF α)/ETO
 - Acute promyelocytic leukemia t(15;17)(q22;q11-12), PML/RAR α and variants
 - Acute myeloid leukemia with abnormal bone marrow eosinophils (inv [16]p13q22) and variants, CBF β /MYH11)
 - 11q23, MLL abnormalities
3. Should severe multilineage dysplasia, prior therapy, and/or prior MDS be included in classification of AML? Yes
4. Should MDS with multilineage dysplasia be a separate category? Yes

LYMPHOID NEOPLASMS

The proposed WHO classification of lymphoid neoplasms adopts the Revised European-American Classification of Lymphoid Neoplasms (REAL), proposed by the International Lymphoma Study Group. This classification is based on the premise that a classification should attempt to define distinct disease entities, using all available information, including morphology, immunophenotype, genetic features, and clinical features. There is no one gold standard, and the importance of various criteria for both definition and diagnosis differs among different diseases. On the basis of experience with using this classification for several years and on input from the committees, several changes were proposed for the WHO version. These include some changes in nomenclature, splitting some categories that were believed to be heterogeneous, and adopting some “provisional” entities as “real.” The proposed classification recognizes B-cell neo-

plasms, T/NK-cell neoplasms, and Hodgkin disease. The T- and B-cell neoplasms are stratified into precursor, or lymphoblastic, neoplasms (acute lymphoblastic leukemia and lymphoblastic lymphoma) and mature (“peripheral”) B- and T-cell neoplasms. The mature B- and T-cell neoplasms are informally grouped according to their major clinical presentations: predominantly disseminated/leukemic, primary extranodal, and predominantly nodal diseases. The pathologists sought input from the clinicians on these changes and on some issues that remain controversial or problematic, such as grading of follicular lymphoma, how to define “Burkitt-like” lymphoma, subclassification of large B-cell lymphomas and mature T-cell lymphomas, and the desirability of clinical groupings of the non-Hodgkin lymphomas.

Precursor Neoplasms

Should the FAB terms (L1, 2, 3) be retained? There was a consensus that these terms are no longer relevant, because L1 and L2 morphology do not predict immunophenotype, genetic abnormalities, or clinical behavior. L3 is generally equivalent to Burkitt lymphoma in leukemic phase and should be diagnosed as such.

Are lymphoblastic leukemias and lymphoblastic lymphomas a single disease with different presentations? There was a consensus that the precursor neoplasms presenting as solid tumors and those presenting with marrow and blood involvement are biologically the same disease but with different clinical presentations. The presence of bone marrow and peripheral blood involvement are principally prognostic factors/staging issues, not classification issues, although the biologic basis for the different clinical presentations is not fully understood. Most precursor lymphoid neoplasms present as leukemia, and thus it was agreed that the classification should retain the term *acute lymphoblastic leukemia*, for the leukemic phase of precursor neoplasms of T and B types (Table 6).

Should genetic abnormalities be included in the classification? Genetic abnormalities are important prognostic factors within precursor B lymphoblastic neoplasms (t[9;22][q34;q11], BCR/ABL; 11q23, MLL; t[1;19][q23;p13], E2A/PBX1; t[12;21][p12;q22]; ETV/CBF α), and pathologists who undertake to di-

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 α
Precursor T-cell acute lymphoblastic leukemia
Burkitt cell leukemia

agnose these neoplasms should be familiar with the types and significance of genetic abnormalities that can be seen. The genetic analysis should be part of (or an addendum to) the pathology report whenever feasible.

Summary

1. Should the FAB terms (L1, 2, 3) be retained?
No
2. Are acute lymphoblastic leukemias and lymphoblastic lymphomas a single disease with different clinical presentations? Yes
 - Retain the term *leukemia* for all precursor T and B types
3. Should cytogenetics be included in classification? Yes
 - As prognostic factors within each subtype
 - t(9;22)(q34;q11), BCR/ABL; 11q23, MLL; t(1;19)(q23;p13), E2A/PBX1; t(12;21)(p12;q22), ETV/CBF α

Mature B and T/NK Neoplasms

As for the precursor neoplasms, the proposed classification considers lymphomas and lymphoid leukemias of the same cell type as one disease with different clinical presentations or stages. For the mature B and T/NK neoplasms, this question is primarily relevant to B-cell chronic lymphocytic leukemia and B-cell small lymphocytic lymphoma. Although patients in some locations may be seen by different physicians based on their presentation (*e.g.*, those presenting with peripheral blood involvement leukemias being seen by hematologists and those presenting with tissue involvement lymphomas by oncologists), there was a consensus that they are biologically the same disease (Table 7).

Follicular Lymphoma

Should the nomenclature be changed to follicular lymphoma? The WHO committee proposed to change the nomenclature from “follicle center lymphoma” to “follicular lymphoma.” The CAC overwhelmingly approved this proposal. For the rare case of purely diffuse lymphoma that seems to be of follicle center origin (predominance of centrocytes, rare centroblasts, BCL2 rearranged), the term *follicle center lymphoma, diffuse* will be retained as a separate category. This diagnosis should be made only when both small and large cells are B cells and preferably with demonstration of some indicator of

follicle center derivation, such as BCL2 rearrangement or CD10 expression.

Should follicular lymphoma be graded by the number of large cells? The following points were made. First, follicular lymphoma of Grade 1 (follicular small cleaved) and Grade 2 (follicular mixed) are more closely related to each other than to Grade 3 (follicular large cell [FLC]), because in sequential biopsies, transitions are seen from Grade 1 (follicular small cleaved) to Grade 2 (follicular mixed) and *vice versa* but rarely from Grade 1 to Grade 3 (FLC). Second, patients with Grade 3 (FLC) tend to have earlier relapses (worse freedom from relapse) than Grades 1 and 2 but similar overall survival, and this inferior freedom from relapse may be obliterated by adriamycin-containing therapy. Third, Grade 3 follicular lymphoma is not the same disease as diffuse large B-cell lymphoma (DLBCL), because it has a higher relapse rate although slightly better overall survival. Finally, pathologists discriminate poorly between follicular lymphoma of Grades 1 and 2 but may be better able to discriminate between these and Grade 3 cases. Several studies suggest that the “Berard” criteria (3) for the diagnosis of Grade 3 follicular lymphoma (more than 15 centroblasts/high power field [HPF]) may best define the group of cases with a potential for early relapses that may be prevented by adriamycin-containing chemotherapy. There was no consensus on whether this is warranted as initial therapy for these patients. It was also noted that other factors than histologic grade affect outcome in patients with follicular lymphoma, including clinical features summarized in the International Prognostic Index and potential biologic markers such as BCL2 expression and *p53* mutations.

In summary, there was a consensus that follicular lymphoma should be graded, at least into two grades, with what is currently recognized as Grade 3 (FLC) being discriminated from lower grade cases. Although there are minor differences in natural history and response to treatment between Grades 1 and 2 follicular lymphoma, there was a consensus that these did not mandate different approaches to treatment and thus were not of great clinical importance. Nonetheless, there was concern that changing the nomenclature would be potentially confusing and that a three-grade system should be retained. The pathologists were encouraged to define clinically relevant and reproducible criteria for such grading. After discussion, the pathologists concluded that because only the Berard cell-counting method (Table 8) has been repeatedly tested in the literature, it should be recommended for use (Grade 1: 0–5 centroblasts/HPF; Grade 2: 6–15 centroblasts/HPF; Grade 3: more than 15 centroblasts/HPF. Ten to 20 HPFs, within different fol-

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

B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
Variant: with monoclonal gammopathy/plasmacytoid differentiation
Hairy cell leukemia
Variant: hairy cell leukemia variant

TABLE 8. Follicular and Mantle Cell Lymphomas: Grading and Variants

Follicular lymphoma
Grades:
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 centroblasts/HPF
Grade 2: 6–15 centroblasts/HPF
Mantle cell lymphoma
Variant: blastoid

HPF, high power field.

licles are counted; these are representative follicles, not selected for those with the most numerous large cells) (4).

Should diffuse areas be reported? Several oncologists believed that diffuse areas in all grades of follicular lymphoma do seem to have an impact on prognosis. There was a consensus that diffuse areas should be reported and quantified according to the recommendations of the REAL classification: predominantly follicular (>75% follicular), follicular and diffuse (25 to 75% follicular), and predominantly diffuse (<25% follicular). However, it is not clear what the implications of these features for treatment would be. In Grade 3 follicular lymphoma, diffuse areas represent areas of DLBCL and should be reported as such (e.g., “follicular lymphoma, Grade 3/3 [75%] with diffuse large B-cell lymphoma [25%],” not “follicular lymphoma, Grade 3, follicular and diffuse.”) The presence of DLBCL in any follicular lymphoma will dictate more aggressive therapy.

Summary

1. Change nomenclature from “follicle center lymphoma” to “follicular lymphoma”? Yes
2. Should it be graded by the number of large cells? Yes
3. Are two grades adequate for clinical practice? Yes
 - But three grades will be used to avoid confusion.
4. What should be method of grading? No consensus
 - Pathologists recommend cell-counting method.
 - Grade 1 (1–5 centroblasts/HPF); Grade 2 (6–15 centroblasts/HPF); Grade 3 (>15 centroblasts/HPF)
5. Should diffuse areas be reported? Yes
6. How should they be quantified? No consensus
 - Pathologists recommended criteria suggested in REAL classification: follicular

(>75% follicular), follicular and diffuse (25 to 75% follicular), predominantly diffuse (<25% follicular).

- Areas of DLBCL should be classified separately. Example of suggested terminology: follicular lymphoma, Grade 3/3 (75%), with DLBCL (25%).

Marginal Zone Lymphomas

Should the term extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) or MALT-type lymphoma be applied only to a lymphoma composed mostly of small cells? What should be the terminology for large-cell lymphoma in a MALT site? The term *high-grade MALT lymphoma*, which is used by some pathologists to denote either transformation of a low-grade MALT lymphoma or any large B-cell lymphoma in a MALT site, is confusing to clinicians, who have come to regard the term *MALT lymphoma* as synonymous with a lesion that may respond to antibiotic therapy for eradication of *Helicobacter pylori*. Because experience indicates that patients with a component of large-cell lymphoma may not respond to antibiotic therapy, the oncologists were concerned that use of this term may result in undertreatment in cases of extranodal large-cell lymphoma. Furthermore, recent data show that the types of cytogenetic abnormalities seen in low-grade MALT lymphomas differ from those seen in primary large-cell lymphoma of the stomach, raising the question of whether these primary lymphomas are really related to low-grade MALT lymphomas. Therefore, the oncologists preferred that the term *MALT lymphoma* be used only for the low-grade lymphoma originally described as “low-grade B-cell lymphoma of MALT.” Areas of large-cell lymphoma, if present, should be separately diagnosed as “DLBCL.” Primary large-cell lymphomas of MALT sites should be diagnosed as “DLBCL,” not as “high-grade MALT lymphoma.”

Should marginal zone/MALT lymphoma be graded by the proportion of large cells? The issue of grading MALT lymphoma has not been extensively studied. Several early reports suggested that cases with up to 25% large cells did not have a worse prognosis than cases with fewer large cells. However, a recent report of patients treated primarily with antibiotics found that the presence of increased transformed cells (5 to 10% with clusters of fewer than 20 cells) conferred a slight but significantly worse prognosis compared with cases with fewer than 5% large cells. Cases with high-grade areas consisting of sheets of blasts (>20 cells) behaved similarly to large-cell lymphoma with no low-grade component. In addition, it was reported at the meeting that the International Non-Hodgkin’s Lymphoma classification project indi-

cated that the presence of more than 5% large cells in an extranodal marginal zone lymphoma conferred a worse prognosis, as did areas of DLBCL. The consensus of the committee was that the data available raise the concern that increased large cells may be of prognostic importance in MALT lymphoma and warrant further study. The WHO classification should specify criteria for grading so that its significance can be tested in future clinical studies. In cases of marginal zone B-cell lymphoma (low-grade MALT lymphoma) with coexisting DLBCL, a separate diagnosis of DLBCL should be made. The principle is therefore similar to that for follicular lymphoma: the tumors are graded according to the number of large cells, but when confluent areas of large cells are present, this indicates transformation to DLBCL.

Are marginal zone lymphomas of nodal and splenic type "real"? There was a consensus that recent data support the recognition that two other types of lymphoma called "marginal zone lymphomas" are distinct both from MALT lymphoma and from each other. Splenic marginal zone lymphoma seems to be the tissue counterpart of splenic lymphoma with villous lymphocytes. Patients typically are older adults with bone marrow and blood involvement and a very indolent clinical course. Nodal marginal zone lymphoma (which often has a prominent monocytoid B-cell component) must be distinguished both from MALT lymphoma with lymph node involvement and from other lymphomas (particularly follicular and mantle cell lymphoma) with a marginal zone pattern or a component of monocytoid B cells. Nodal marginal zone lymphoma seems to have a high rate of early relapse and overall survival similar to or slightly worse than that of follicular lymphoma.

Summary

1. Should the term *extranodal marginal zone B-cell lymphoma of MALT*, or *MALT-type lymphoma*, be applied only to a lymphoma composed mostly of small cells and not to large-cell lymphoma in a MALT site? Yes
2. Should the term *high-grade MALT lymphoma* be used? No
 - Suggested terminology: DLBCL (\pm areas of marginal zone/MALT-type lymphoma)
3. Should extranodal marginal zone B-cell lymphoma of MALT type be further graded/stratified based on number of large cells? Research question
 - Criteria should be given so that additional studies can be done.
4. Are nodal and splenic marginal zone lymphomas distinct diseases that should be recognized and defined in the classification? Yes

B-Cell Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Are B-cell chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) one disease at different stages? As for the precursor neoplasms and Burkitt lymphoma, the committee agreed with the pathologists that B-CLL and SLL are one disease at different stages, not two separate entities, and should be listed together in the classification (Table 7).

Are cases of B-CLL with plasmacytoid differentiation (lymphoplasmacytoid immunocytoma in the Kiel Classification) a different disease from typical CLL? Data from several groups using the Kiel Classification suggest that plasmacytoid differentiation may be an adverse prognostic factor in B-CLL; the committee believed that the available data do not support calling it a different disease and that further study is needed to determine whether plasmacytoid differentiation is an adverse prognostic factor in CLL. Therefore, recognition of this feature is not required for diagnosis for clinical purposes, but criteria for diagnosing plasmacytoid differentiation should be agreed on if possible for future studies.

Summary

1. Are B-CLL and SLL one disease at different stages? Yes
2. Is plasmacytoid differentiation an indication of a different disease? No
3. Is plasmacytoid differentiation a prognostic factor? Research question

Mantle Cell Lymphoma

Should mantle cell lymphoma be subclassified/graded for clinical purposes? A number of studies have found morphologic heterogeneity in mantle cell lymphoma (MCL) in both pattern and cytology and have suggested that some features may predict outcome. For example, cases with a mantle zone pattern have been less aggressive in some studies but not in others, and cases with blastic or blastoid morphology have had a worse prognosis in some reports. It was the consensus of the committee that because no effective therapy exists for any type of MCL, stratification by morphologic features is not required for clinical diagnostic purposes at this time. However, the different cytologic types and patterns will be included in the text of the classification (2) so that variant cases will be recognized as MCL for diagnosis and graded similarly for research studies (Table 8).

Summary

1. Should MCL be subclassified/graded by cytology for clinical purposes? No
2. Should MCL be subclassified/graded by pattern for clinical purposes? No

- Different cytologic types and patterns should be included so that they will be recognized as MCL for diagnosis and graded similarly for research.

Large B-cell Lymphoma and Burkitt-Like Lymphoma

Should morphologic subclassification of DLBCL be required? There was a consensus of the CAC that neither biologic nor clinical data at present support a requirement for subclassification of DLBCL according to the criteria of the Working Formulation or the Kiel Classification. Data from the Kiel group suggest that immunoblastic lymphoma as defined in the updated Kiel Classification (>90% immunoblasts) has a worse prognosis than centroblastic lymphoma. Other data suggest that staining for bcl-6 (centroblastic) and syndecan-1/CD138 (immunoblastic) or evidence of BCL6 rearrangement (centroblastic) may help to discriminate between them. Nonetheless, neither reliable pathologic or biologic criteria for subclassification nor distinctive therapies that can be recommended for clinical practice are available at this time. For these reasons, the committee believed that these categories should remain optional at this time. However, there was agreement that the pathologists should develop criteria for subclassification so that these categories can be tested in future clinical studies (Table 9).

Should “Burkitt-like” or “non-Burkitt” lymphoma be a subtype of DLBCL, a subtype of Burkitt lymphoma, or a distinct category? What should be defining criteria? The pathologists proposed to define *Burkitt-like* lymphoma as a subtype of large B-cell lymphoma. However, there was a clear consensus among the oncologists that this would be a mistake. There are abundant data indicating that in children, cases classified as Burkitt-like (or non-Burkitt) behave identically to Burkitt lymphoma and would be undertreated if treated as large B-cell lymphoma. In adults, the biology of cases classified as Burkitt-like is less clear, but this may reflect the heterogeneity of the diagnostic criteria. In the International Non-Hodgkin’s Lymphoma study, Burkitt-like was a

nonreproducible category, with only approximately 50% agreement among the pathologists; the major areas of overlap were DLBCL and Burkitt lymphoma. The oncologists urged that the category of Burkitt-like lymphoma be reserved for tumors that should be treated “like Burkitt lymphoma”—that is, very high-grade tumors. The committee concluded that Burkitt-like lymphoma should be listed as a morphologic variant of Burkitt lymphoma in the WHO classification. The term *atypical Burkitt lymphoma* was proposed for this variant; however, the Steering Committee subsequently decided that the term *Burkitt-like* was preferable, because the relationship to Burkitt lymphoma is not known in all cases. Thus, the category of Burkitt lymphoma will include classic Burkitt lymphoma and a variant, Burkitt-like lymphoma. In addition, three subcategories—endemic, nonendemic, and immunodeficiency associated—were proposed to reflect the major clinical and genetic subtypes of this disease.

At present, there are no readily available immunophenotypic criteria that can be used in this differential diagnosis. However, participants observed that probably both the morphology and the biology of Burkitt lymphoma are defined by the presence of cMYC rearrangement and overexpression, which results in all cells being perpetually in cycle. The gold standard for the diagnosis of Burkitt lymphoma should be the presence of the t(8;14)(q24;q32) and its variants or cMYC rearrangement. Cytogenetic analysis is recommended in all leukemic cases. If cytogenetic or Southern blot analysis is not available in solid tumors, it seems likely that the most reasonable surrogate for cMYC rearrangement is proliferation fraction. Therefore, it was suggested that cases in which cytogenetic analysis is not available should not be diagnosed as Burkitt lymphoma or Burkitt-like lymphoma without a Ki-67 fraction close to 100%. Thus, the definition of Burkitt-like lymphoma is a lymphoma that morphologically resembles Burkitt lymphoma but has more pleomorphism or large cells than classical Burkitt lymphoma and has a proliferation fraction of more than 99%.

Do we need separate categories for clinical subtypes of DLBCL? There are multiple distinct clinical presentations of DLBCL, several of which have unique clinical behavior. These include mediastinal/thymic large B-cell lymphoma, primary central nervous system (CNS) lymphoma, and primary effusion lymphoma. Of particular concern to pathologists is the category of cutaneous B-cell lymphoma, most of which have a very indolent clinical course. One category—marginal zone/MALT lymphoma—is easily recognized by pathologists as a low-grade lymphoma. However, the other major category, called *cutaneous follicle center lymphoma* in the recently proposed European Organization for

TABLE 9. Diffuse Large B-Cell Lymphoma: Morphologic Variants and Subtypes

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

Research and Treatment of Cancer (EORTC) classification, has a range of morphology, from a clearly low-grade lesion resembling nodal follicular lymphoma to a diffuse proliferation with numerous large cells that may be called DLBCL by pathologists. This type of lymphoma, which typically is localized to the head and trunk, responds well to local therapy (excision or radiation), and typically does not disseminate to lymph nodes, composed 70% of cutaneous B-cell lymphomas in the EORTC study. There is concern that if its distinctive histologic and clinical features are not recognized by both pathologists and oncologists, these patients will be overtreated with aggressive chemotherapy.

The consensus of the committee was that separate classifications of lymphomas at specific extranodal sites were not needed for clinical purposes. However, the site of involvement should be clearly stated in the pathology report, and oncologists are obliged to understand the distinctive clinical features of lymphomas at various sites. Distinct entities such as primary mediastinal (thymic) B-cell lymphoma, primary effusion lymphoma, and intravascular lymphoma will be described in the text as subtypes of DLBCL (Table 9). The committee recommended that the distinctive clinical features of B-cell lymphomas in the skin be indicated in the text describing each lymphoma subtype.

Summary

1. Should morphologic subclassification of DLBCL be required? No
 - Criteria for subclassification should be standardized for future studies.
2. Should the category of “Burkitt-like” be a subtype of large B-cell lymphoma? No
 - Burkitt-like lymphoma will be considered a variant of Burkitt lymphoma.
 - Major criteria include 1) morphology intermediate between Burkitt lymphoma and large-cell lymphoma, 2) t(8;14)(q24;q32) and variants, cMYC rearrangement, or 3) proliferation fraction (Ki-67) more than 99%.
3. Do we need separate categories for clinical subtypes of DLBCL? No
 - Location should be indicated in report.

Lymphomas in Immunodeficiency States: Do We Need a Separate Classification?

Most lymphomas that occur in immunodeficiency states are also seen in nonimmunosuppressed patients but have some distinctive features in patients immunodeficiency. For example, in patients with HIV-positive status, primary CNS lymphoma is always Epstein-Barr virus (EBV) positive, in contrast to sporadic CNS lymphoma. Hodgkin disease is more aggressive and always EBV positive

in patients with HIV-positive status. The recently described primary effusion lymphoma, which was initially thought to be unique to patients with HIV-positive status, has been reported in patients with HIV-negative status as well. T-cell lymphomas in patients with HIV-positive status also do not seem to be distinctive. A recently described plasmablastic lymphoma is distinctive, and its relationship to myeloma remains to be determined.

The polymorphic posttransplant lymphoproliferative disorders (PTLD) seem to be a unique form of lymphoproliferation that does not occur in immunologically normal individuals. It was suggested that EBNA-2 expression in these lesions indicates that the proliferation is EBV driven and may respond to reduced immunosuppression.

In summary, the committee suggested that a separate classification was not needed for immunodeficiency-associated lymphomas but that the specific types of lymphomas that occur in immunodeficiency states and their distinctive features in these conditions should be indicated both in the text and in a table. In addition, the pathologists believed that a separate classification of PTLD would be useful, because of their distinctive biologic and clinical features (Table 3).

Summary

- Do we need a separate classification for lymphomas in immunodeficiency states? No
- Note the frequency of specific types in immunodeficiency states.
 - PTLD are distinctive and need a separate classification.
 - EBV status may be important in determining prognosis/treatment.

Are Clinical Syndromes Integral to the Definition of T/NK-Cell Neoplasms?

Many distinct T- and/or NK-cell diseases have a range of cytologic composition (small to large to anaplastic). Immunophenotypic variation exists within disease entities, and many antigens are shared by different diseases. Specific cytogenetic features are not defined for most entities, and even T-cell receptor types ($\alpha\beta$ versus $\gamma\delta$) or T versus NK lineage is not sufficient to define distinct disease entities. To a greater extent than is appreciated for B-cell neoplasms, it seems that clinical syndromes, and particularly location (nodal versus extranodal and specific extranodal sites), are important in determining the biologic behavior of the disease. The committee agreed that clinical syndromes seem to be integral to the definition of T- and NK-cell neoplasms.

Should Peripheral T-Cell Lymphoma, Unspecified, Be Subclassified (According to the Kiel Classification) for Clinical Purposes?

On the basis of the available data, there seems to be no immediate justification or clear criteria for recognizing cytologic subtypes within this broad category. However, given the marked differences in clinical behavior between primary extranodal T/NK-cell lymphomas and primary nodal lymphomas, it is likely to be clinically relevant to subdivide the “unspecified” category into nodal and extranodal types. Both pathologists and oncologists will need to continue to address this area in further studies (Tables 13–15).

Summary

1. Are clinical syndromes integral to the definition of peripheral T/NK-cell neoplasms? Yes
2. Is cytologic subclassification of peripheral T-cell lymphoma required for clinical purposes? No

Anaplastic Large Cell Lymphoma

Should cutaneous and systemic anaplastic large cell lymphoma (ALCL) be considered one disease or two? What should be the terminology for the cutaneous type? There is evidence that most cases of ALCL of T-cell type presenting with disease localized to the skin are a different disease from systemic ALCL: the clinical course is indolent, they lack the t(2;5)(p23;q35) and are ALK protein negative, and seem to form a spectrum with lymphomatoid papulosis. Although some members of the committee believed that the clinical course was not predictably indolent, there was general agreement that at least for the purposes of further study, cutaneous and systemic ALCL should be considered distinct categories. There was significant concern, however, about the proposed term *primary CD30+ cutaneous lymphoproliferative disorder*—a term that includes lymphomatoid papulosis, cutaneous ALCL, and CD30+ cutaneous T-cell lymphomas that do not have typical “anaplastic” morphology. Oncologists believed that including lymphomatoid papulosis in a classification of lymphomas would imply to patients and insurers that this is a malignancy, whereas it typically has a benign clinical course.

In conclusion, the committee agreed that the entity, primary cutaneous ALCL, should be included in the list of neoplasms and that a discussion of *CD30+ cutaneous lymphoproliferative diseases* should be included in the text with a discussion of lymphomatoid papulosis and borderline lesions. Because of the difficulty in predicting by morphology alone which disease the patient has, pathologists will often be forced to use the term *CD30+*

TABLE 10. Burkitt Lymphoma: Morphologic Variants and Subtypes

Burkitt lymphoma, morphologic variants
Burkitt-like
With plasmacytoid differentiation (AIDS associated)
Burkitt lymphoma, subtypes (clinical and genetic)
Endemic
Sporadic
Immunodeficiency associated

cutaneous lymphoproliferative disease on the pathology reports, with the understanding that clinical criteria must be added to determine whether the patient has a locally progressive disease that requires treatment (ALCL) or a relapsing condition that needs no treatment (lymphomatoid papulosis).

What is the gold standard for defining ALCL? Given the recent availability of an antibody to the ALK protein, which is highly associated with the t(2;5)(p23;q35), the question raised was whether this can be used as the defining criterion for ALCL. Clinically, cases with the t(2;5) and/or ALK positivity seem to represent a homogeneous group with a relatively good prognosis. However, others observed that experience with ALK antibodies is limited and they are only now becoming commercially available. In addition, there are cases with typical morphology and immunophenotype that are ALK or t(2;5) negative. The committee concluded that a single gold standard for the diagnosis of ALCL does not exist; the diagnosis requires both morphology and immunophenotype, and at least at present, restricting the diagnosis to ALK-positive cases does not seem to be justified. It was suggested that ALK staining be done in all cases to the extent possible and that cases be designated as ALCL, ALK positive, or ALK negative, at least for research purposes. In addition, pathologists need to be aware of the broad morphologic spectrum of ALCL.

Summary

1. Is cutaneous ALCL different from systemic ALCL? Probably
 - Distinction between them is not always straightforward, and cutaneous type is not always indolent.

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

TABLE 12. Immunosecretory Disorders (Clinical Manifestations of Diverse Lymphoid Neoplasms)

Clinical Syndrome	Underlying Neoplasm
Waldenstrom's macroglobulinemia	Lymphoplasmacytic lymphoma
Heavy chain diseases (HCD)	
gamma HCD	Lymphoplasmacytic lymphoma
alpha HCD	Extranodal marginal zone lymphoma (immunoproliferative small intestinal disorder)
Mu HCD	B-cell chronic lymphocytic leukemia
Immunoglobulin deposition diseases	
Systemic light chain disease	Plasma cell myeloma, monoclonal gammopathy
Primary amyloidosis	Plasma cell myeloma, monoclonal gammopathy

2. Should lymphomatoid papulosis appear in the list of lymphoid neoplasms? No
 - It should be discussed in the text along with borderline cases.
3. Is there a gold standard for the diagnosis of ALCL? Not yet
 - The morphologic spectrum of ALCL needs to be better understood by pathologists.
 - Cases should be listed as ALK positive or ALK negative for research.

Hodgkin Disease

Should grading of nodular sclerosis be required for clinical use? Data on the clinical impact of grading nodular sclerosis Hodgkin disease according to the British National Lymphoma Investigation criteria (Grade 1 = few RS cells; Grade 2 = many RS cells) have shown conflicting results, with some studies showing that Grade 2 cases are associated with a worse outcome and others showing no difference in outcome. The committee recommended that grading not be required for clinical purposes in routine diagnosis but that the classification include clear criteria so that this question can be tested in future studies.

Nomenclature: Hodgkin disease or Hodgkin lymphoma? Because it is now clear that Hodgkin disease is a clonal proliferation of (in most cases) B cells and therefore qualifies as a lymphoma, the pathologists proposed that the name be changed to Hodgkin lymphoma. Opinion of the committee was divided on this score; some believed that patients become confused as to whether they have a lymphoma or not when the term *disease* is used, and others stood on tradition and resisted unnecessary change. No consensus was reached.

Is lymphocyte-rich classical Hodgkin disease a "real" subtype? Very few clinical data exist on this subtype, proposed as "provisional" in the REAL classification. The committee agreed that it was important to separate these cases from nodular lymphocyte predominance Hodgkin disease for clinical purposes and that it would be valuable to separate them from other types of classical HD for clinical research purposes.

Is anaplastic large cell lymphoma, Hodgkin like, real? The pathologists proposed to drop this provisional category from the REAL classification, believing that there is probably no true biologic borderline between Hodgkin disease (in most cases a B-cell process) and ALCL (in most cases a T-cell process). Some cases of ALCL may have a nodular growth pattern and areas of fibrosis and thus *resemble* Hodgkin disease of nodular sclerosis type. Some cases of nodular sclerosis Hodgkin disease may have increased numbers of malignant cells and therefore *resemble* ALCL. However, this resemblance does not indicate a biologic relationship. Pathologists should strive to resolve morphologically difficult cases by immunophenotyping and, if necessary, molecular genetic studies. In a case that is morphologically on the borderline between Hodgkin disease and ALCL, expression of CD15 with or without B-cell antigens favors Hodgkin disease, whereas absence of CD15 and expression of T-cell antigens or ALK protein favor ALCL. Detection of T-cell receptor gene or NPM/ALK rearrangement would confirm T-cell lymphoma, and absence of rearrangements would favor Hodgkin disease. Cases that cannot be resolved by a combination of morphology, immunophenotype, and genetic studies should be considered unclassifiable. Clinical judgment should be used to determine whether to rebiopsy or to treat with a regimen that would be suitable for both Hodgkin disease and ALCL.

Summary

1. Should grading of nodular sclerosis Hodgkin disease be required for clinical use? No
 - Criteria need to be clearly defined for future studies.
2. Should lymphocyte-rich classical Hodgkin disease be a separate category? Yes
 - Clinical features need further study.
3. Is ALCL-Hodgkin disease-like a real entity? No
 - Pathologists should use immunophenotyping and molecular genetic techniques to classify morphologically borderline cases as

either Hodgkin disease or ALCL; unresolved cases should be called unclassifiable.

4. Should we change the name from Hodgkin disease to lymphoma? No consensus
 - Proposal: allow both (Hodgkin disease/Hodgkin lymphoma)

Clinical Groupings of B- and T/NK-Cell Lymphomas

Are clinical groupings of B- and T/NK-cell lymphomas useful for clinical practice? The committee concluded that grouping the B- and T/NK-cell neoplasms into prognostic categories would serve no clear purpose and could hamper understanding of the specific features of some of the diseases. There are no groups of diseases that require identical treatment, and if treatment must be individualized to a specific disease, grouping serves no purpose and may be misleading. The entities listed in the classification are clearly defined and clinically relevant, and it is necessary for oncologists and pathologists dealing with these diseases to understand each of them.

Is a shorter list of diseases necessary for clinicians? The committee also discussed whether a shorter list of common diseases should be prepared for clinical use. There was a clear consensus that the complete list of neoplasms should have more common entities highlighted, to draw the attention of nonexperts to the diseases that they are likely to encounter in practice. Opinion was split on the need for a “short list,” and a poll taken after the meeting showed a majority of the oncologists favoring one comprehensive list with common entities highlighted.

Summary

1. Are clinical groupings of B- and T/NK-cell lymphomas necessary or useful? No
2. Should common entities be indicated in bold? Yes
3. Should a short list of common entities be included for clinicians? No

Unclassifiable Hematologic Malignancies

Even with the advances in immunophenotyping and genetic analysis, some hematologic malignan-

TABLE 13. T-Cell Neoplasms, Disseminated Leukemic Types: Variants

T-cell prolymphocytic leukemia, morphologic variants
Small cell
Cerebriform cell
Adult T-cell leukemia/lymphoma (HTLV1+), clinical variants
Acute
Lymphomatous
Chronic
Smoldering
Hodgkin-like

TABLE 14. Peripheral T-Cell Neoplasms, Primary Extranodal Types: Variants and Subtypes

Mycosis fungoides variants
Pagetoid reticulosis
Mycosis fungoides-associated follicular mucinosis
Granulomatous slack skin disease
Primary cutaneous CD-30 positive T-cell lymphoproliferative disorders
Lymphomatoid papulosis (type A and B)
Primary cutaneous anaplastic large cell lymphoma
Borderline lesions

TABLE 15. Peripheral T-Cell Neoplasms, Predominantly Nodal Types: Variants

Peripheral T-cell lymphoma (not otherwise categorized), variants
Lymphoepithelioid (Lennert's)
T-zone
Anaplastic large cell lymphoma T/null cell type, variants
Lymphohistiocytic
Small cell

TABLE 16. Proposed Categories of Unclassifiable Hematologic Malignancies

Hematologic malignancy, unclassifiable
Myeloid neoplasm, unclassifiable
Myeloproliferative disease, unclassifiable
Myelodysplastic syndrome, unclassifiable
Acute myeloid leukemia, unclassifiable
Lymphoid neoplasm/lymphoma, unclassifiable
B-cell lymphoma, unclassifiable
T-cell lymphoma, unclassifiable
Hodgkin disease, unclassifiable
Histiocytic neoplasm, unclassifiable

cies still defy classification. A case may be unclassifiable because of an inadequate tissue sample, because special studies are not available, because the tissue is poorly preserved, or because even with complete analysis it does not fit into one of the categories recognized in the classification. For each case, the reason for the inability to classify it should be stated in the pathology report. Suggested categories and terminology for unclassifiable cases are listed in Table 16.

CONCLUSIONS

The committee concluded that the approach to the classification of hematologic malignancies proposed by the International Lymphoma Study Group in the REAL classification and adopted now in the WHO classification represents a significant advance in our ability to identify and treat specific disease entities. This approach leaves room for identifying new entities and subtypes and for incorporating new data into diagnostic criteria, disease definition, and nomenclature. It has also produced a new and exciting degree of cooperation and communication between oncologists and pathologists from around the world that should facilitate accumulation of new knowledge and that will hopefully continue in the future. After the WHO classification is com-

pleted, it will be important to develop a mechanism for updating it, to avoid the confusion that has often resulted from the existence of multiple classifications.

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