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EDITORIAL

Advances in the Classification of Myeloid and Lymphoid Neoplasms

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The diagnosis, classification and treatment of hematopoietic neoplasms requires a precise definition of the individual entities that configure the broad spectrum of these diseases. Since the introduction of the Revised European American Lymphoma (REAL) classification in 1994, the approach to classification of these neoplasms incorporates clinical, morphologic, immunophenotypic and genetic information. While underlying cell lineage is a starting point, when possible, the normal cellular counterpart from which the tumor originates is defined. This combined approach has gained further relevance with the introduction of targeted therapies. Following publication of the REAL classification [1], the International Agency for Research on Cancer (IARC), in anticipation of developing the 3rd edition World Health Organization (WHO) classification of Hematolymphoid Neoplasm, approached Elaine Jaffe, contributor to the REAL classification and then President of the Society for Hematopathology (SH), asking the Society to partner with them to develop a similar approach for the classification of hematopoietic neoplasms. The partnership was ultimately between IARC, SH and the European Association for Haematopathology (EAHP). The Societies recognized that clinical features were also a key feature for accurate disease definition, and that input from treating physicians of these neoplasms was essential for any classification to be relevant and broadly accepted. World-wide consensus was regarded as critical after decades of different classification systems driven by individuals or regional groups. The SH and EAHP undertook planning for a Clinical Advisory Committee (CAC) meeting, which was supported by funds raised by the Societies, before developing a classification. In advance of the CAC, the participating pathologists developed key questions regarding the classification and during the CAC additional pathologists as well as hematologists, oncologists and geneticists provided input and discussion to arrive at a consensus. After the CAC, the pathologists worked to resolve final issues related to the CAC recommendations and published the classification in review papers prior to formal publication of the associated WHO "Blue Book." The first such CAC took place in Arlie House, Virginia in 1997 and ultimately resulted in the 2001 3rd edition WHO classification, the first widely accepted WHO classification of hematopoietic tumors. This successful partnership between SH, EAHP and IARC continued with a similar process including the organization of CACs in 2007 and 2014, resulting in publications of the CAC conclusions in specific articles and ultimately with publication of the 4th edition and revised 4th edition WHO Blue Books in 2008 and 2017.

In 2020, Ian Cree, Head of the Evidence Synthesis and Classification Branch of the IARC in charge of the publication of the WHO blue books, notified SH and EAHP that IARC was ending the successful partnership with SH and EAHP for the 5th edition WHO classification of hematopoietic tumors and that they would no longer follow the process described above for the three prior books. The Executive Committees of the SH and EAHP together with many leaders in the hematopathology, hematology, oncology and genetics community considered that the proper development of a meaningful classification of these neoplasms required a similar process of discussion and consensus as developed for the three previous WHO classifications. Therefore, they organized different multidisciplinary working groups that culminated in the CAC meeting held in Chicago in September 2021. The CAC was followed by publication of the International Consensus

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Classification (ICC) of Myeloid and Lymphoid Neoplasms in two manuscripts [2, 3], (Table 1) as well as two additional manuscripts on the genomic approaches to these tumors [4, 5]. The ICC represents the natural progression of the prior WHO classifications, using the same approach with modification of previously described entities, and recognition of new entities, where relevant. Broad expert review and consensus were key to all conclusions.

Table 1 The International Consensus Classification of Myeloid and Lymphoid Neoplasms

Myeloproliferative neoplasms
Chronic myeloid leukemia
Polycythemia vera
Essential thrombocythemia
Primary myelofibrosis
Early/prefibrotic primary myelofibrosis
Overt primary myelofibrosis
Chronic neutrophilic leukemia
Chronic eosinophilic leukemia, not otherwise specified
Myeloproliferative neoplasm, unclassifiable
Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions
Myeloid/lymphoid neoplasm with *PDGFRA* rearrangement
Myeloid/lymphoid neoplasm with *PDGFRB* rearrangement
Myeloid/lymphoid neoplasm with *FGFR1* rearrangement
Myeloid/lymphoid neoplasm with *JAK2* rearrangement
Myeloid/lymphoid neoplasm with *FLT3* rearrangement
Myeloid/lymphoid neoplasm with *ETV6::ABL1*
Mastocytosis
Myelodysplastic/myeloproliferative neoplasms
Chronic myelomonocytic leukemia
- Clonal monocytosis of undetermined significance
Atypical chronic myeloid leukemia
Myelodysplastic/myeloproliferative neoplasm with thrombocytosis and *SF3B1* mutation
- Myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis, NOS
Myelodysplastic/myeloproliferative neoplasm, NOS
- Myelodysplastic/ myeloproliferative neoplasm with isolated isochromosome (17q)
Pre-malignant clonal cytopenias and myelodysplastic syndromes
Clonal cytopenia of undetermined significance and other clonal cytopenias
Myelodysplastic syndrome with mutated *SF3B1*
Myelodysplastic syndrome with del(5q)
Myelodysplastic syndrome with mutated *TP53*
Myelodysplastic syndrome, not otherwise specified (MDS, NOS)
MDS, NOS without dysplasia
MDS, NOS with single lineage dysplasia
MDS, NOS with multilineage dysplasia
Myelodysplastic syndrome with excess blasts
Myelodysplastic syndrome /acute myeloid leukemia (MDS/AML)
MDS/AML with mutated *TP53*
MDS/AML with myelodysplasia-related gene mutations
MDS/AML with myelodysplasia-related cytogenetic abnormalities
MDS/AML, not otherwise specified
Pediatric and/or germline mutation-associated disorders
Juvenile myelomonocytic leukemia
Juvenile myelomonocytic leukemia-like neoplasms
Noonan syndrome-associated myeloproliferative disorder
Refractory cytopenia of childhood

Table 1 (continued)

Hematologic neoplasms with germline predisposition
Acute myeloid leukemias
Acute promyelocytic leukemia (APL) with t(15;17)(q24.1;q21.2)/*PML*::*RARA*
APL with other *RARA* rearrangements
AML with t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*
AML with t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*
AML with other *KMT2A* rearrangements
AML with t(6;9)(p22.3;q34.1)/*DEK*::*NUP214*
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*; *MECOM*(*EVI1*)
AML with other *MECOM* rearrangements
AML with other rare recurring translocations (see Supplemental Table 5)
AML with t(9;22)(q34.1;q11.2)/*BCR*::*ABL1*
AML with mutated *NPM1*
AML with in-frame bZIP *CEBPA* mutations
AML and MDS/AML with mutated *TP53*
AML and MDS/AML with myelodysplasia-related gene mutations
AML with myelodysplasia-related cytogenetic abnormalities
AML not otherwise specified (NOS)
Myeloid Sarcoma
Myeloid proliferations associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasm
Acute leukemia of ambiguous lineage
Acute undifferentiated leukemia
Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); *BCR::ABL1*
MPAL, with t(v;11q23.3); *KMT2A* rearranged
MPAL, B/myeloid, NOS
MPAL, T/myeloid, NOS
B-lymphoblastic leukemia/lymphoma
B-acute lymphoblastic leukemia (B-ALL)
B-ALL with recurrent genetic abnormalities
B-ALLwith t(9;22)(q34.1;q11.2)/*BCR::ABL1*
with lymphoid only involvement
with multilineage involvement
B-ALLwith t(v;11q23.3)/*KMT2A* rearranged
B-ALL with t(12;21)(p13.2;q22.1)/*ETV6::RUNX1*
B-ALL, hyperdiploid
B-ALL, low hypodiploid
B-ALL, near haploid
B-ALL with t(5;14)(q31.1;q32.3)/*IL3::IGH*
B-ALL with t(1;19)(q23.3;p13.3)/*TCF3::PBX1*
B-ALL, *BCR*::*ABL1*–like, ABL-1 class rearranged
B-ALL, *BCR*::*ABL1*–like, JAK-STAT activated
B-ALL, *BCR*::*ABL1*–like, NOS
B-ALL with iAMP21

Table 1 (continued)

B-ALL with *MYC* rearrangement
B-ALL with *DUX4* rearrangement
B-ALL with *MEF2D* rearrangement
B-ALL with *ZNF384(362)* rearrangement
B-ALL with *NUTM1* rearrangement
B-ALL with *HLF* rearrangement
B-ALL with *UBTF::ATXN7L3/PAN3,CDX2* ("CDX2/UBTF")
B-ALL with mutated *IKZF1* N159Y
B-ALLwith mutated *PAX5* P80R
Provisional entity: B-ALL, *ETV6::RUNX1*-like
Provisional entity: B-ALL, with *PAX5* alteration
Provisional entity: B-ALL, with mutated *ZEB2* (p.H1038R)/IGH::*CEBPE*
Provisional entity: B-ALL, *ZNF384* rearranged-like
Provisional entity: B-ALL, *KMT2A* rearranged-like
B-ALL, NOS
T-lymphoblastic leukemia/lymphoma
Early T-cell precursor ALL with *BCL11B* rearrangement
Early T-cell precursor ALL, NOS
T-ALL, NOS
Provisional entities
Provisional entity: Natural killer (NK) cell ALL
Mature B-cell neoplasms
Chronic lymphocytic leukemia /small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis
CLL type
Non-CLL type
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic B-cell lymphoma/leukemia, unclassifiable
Splenic diffuse red pulp small B-cell lymphoma
Hairy cell leukemia-variant
Lymphoplasmacytic lymphoma
Waldenström macroglobulinemia
IgM monoclonal gammopathy of undetermined significance (MGUS)
IgM MGUS, plasma cell type
IgM MGUS, NOS
Primary cold agglutinin disease
Heavy chain diseases
Mu heavy chain disease
Gamma heavy chain disease
Alpha heavy chain disease
Plasma cell neoplasms
Non-IgM monoclonal gammopathy of undetermined significance
Multiple myeloma (Plasma cell myeloma)

Table 1 (continued)

Multiple myeloma NOS
Multiple myeloma with recurrent genetic abnormality
Multiple myeloma with *CCND* family translocation
Multiple myeloma with *MAF* family translocation
Multiple myeloma with *NSD2* translocation
Multiple myeloma with hyperdiploidy
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Monoclonal immunoglobulin deposition diseases
Immunoglobulin light chain amyloidosis (AL)
Localized AL amyloidosis
Light chain and heavy chain deposition disease
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Primary cutaneous marginal zone lymphoproliferative disorder
Nodal marginal zone lymphoma
Pediatric nodal marginal zone lymphoma
Follicular lymphoma
In situ follicular neoplasia
Duodenal-type follicular lymphoma
BCL2-R negative, CD23-positive follicle center lymphoma
Primary cutaneous follicle center lymphoma
Pediatric-type follicular lymphoma
Testicular follicular lymphoma
Large B-cell lymphoma with *IRF4* rearrangement
Mantle cell lymphoma
In situ mantle cell neoplasia
Leukemic non-nodal mantle cell lymphoma
Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS)
Germinal center B-cell subtype
Activated B-cell subtype
Large B-cell lymphoma with 11q aberration
Nodular lymphocyte predominant B-cell lymphoma
T cell/histiocyte rich large B-cell lymphoma
Primary DLBCL of the central nervous system
Primary DLBCL of the testis
Primary cutaneous DLBCL, leg type
Intravascular large B-cell lymphoma
HHV-8 and EBV-negative primary effusion-based lymphoma
EBV-positive mucocutaneous ulcer
EBV-positive DLBCL, NOS
DLBCL associated with chronic inflammation
Fibrin-associated DLBCL
Lymphomatoid granulomatosis
EBV-positive polymorphic B-cell lymphoproliferative disorder, NOS
ALK-positive large B-cell lymphoma

Table 1 (continued)

Plasmablastic lymphoma
HHV8-associated lymphoproliferative disorder
Multicentric Castleman disease
HHV8- positive germinotropic lymphoproliferative disorder
HHV8- positive DLBCL, NOS
Primary effusion lymphoma
Burkitt lymphoma
High-grade B-cell lymphoma, with *MYC* and *BCL2* rearrangements
High-grade B-cell lymphoma with *MYC* and *BCL6* rearrangements
High-grade B-cell lymphoma, NOS
Primary mediastinal large B-cell lymphoma
Mediastinal gray-zone lymphoma
Classic Hodgkin lymphoma
Nodular sclerosis classic Hodgkin lymphoma
Lymphocyte-rich classic Hodgkin lymphoma
Mixed cellularity classic Hodgkin lymphoma
Lymphocyte-depleted classic Hodgkin lymphoma
Mature T- and NK-cell neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
Adult T-cell leukemia/lymphoma
EBV-positive T/NK LPD of childhood
Hydroa vacciniforme LPD
Classic
Systemic
Severe mosquito bite allergy
Chronic active EBV disease (T and NK-cell phenotype)
Systemic EBV-positive T-cell lymphoma of childhood
Extranodal NK/T-cell lymphoma, nasal type
Aggressive NK cell leukemia
Primary nodal EBV-positive T/NK-cell lymphoma
Enteropathy-associated T-cell lymphoma
Type II refractory celiac disease
Monomorphic epitheliotropic intestinal T-cell lymphoma
Intestinal T-cell lymphoma, NOS
Indolent clonal T-cell lymphoproliferative disorder of the gastrointestinal tract
Indolent NK cell lymphoproliferative disorder of the gastrointestinal tract
Hepatosplenic T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous small/medium CD4-positive T-cell lymphoproliferative disorder
Subcutaneous panniculitis-like T-cell lymphoma

Table 1 (continued)

Primary cutaneous gamma-delta T-cell lymphoma
Primary cutaneous acral CD8- positive T-cell lymphoproliferative disorder
Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma
Peripheral T-cell lymphoma, NOS
Follicular helper T-cell lymphoma
Follicular helper T-cell lymphoma, angioimmunoblastic type (Angioimmunoblastic T-cell lymphoma)
Follicular helper T-cell lymphoma, follicular type
Follicular helper T-cell lymphoma, NOS
Anaplastic large cell lymphoma, ALK-positive
Anaplastic large cell lymphoma, ALK-negative
Breast implant-associated anaplastic large cell lymphoma
Immunodeficiency-associated lymphoproliferative disorders
Post-transplant lymphoproliferative disorders (PTLD)
Plasmacytic hyperplasia PTLD
Infectious mononucleosis PTLD
Florid follicular hyperplasia PTLD
Polymorphic PTLD
Monomorphic PTLD (B- and T/NK-cell types)
Classic Hodgkin lymphoma PTLD
Other iatrogenic immunodeficiency associated lymphoproliferative disorders
Histiocytic and dendritic cell neoplasms
Histiocytic sarcoma
Langerhans cell histiocytosis
Langerhans cell sarcoma
Indeterminate dendritic cell histiocytosis
Interdigitating dendritic cell sarcoma
ALK-positive histiocytosis
Disseminated juvenile xanthogranuloma
Erdheim/Chester disease
Rosai-Dorfman-Destombes disease
Follicular dendritic cell sarcoma
Fibroblastic reticular cell sarcoma
EBV-positive inflammatory follicular dendritic cell/fibroblastic reticular cell tumor

This Annual Review Issue further expands on the International Consensus Classification of Myeloid and Lymphoid Neoplasms, providing more in-depth descriptions of the entities with a focus on the pathologic aspects of the disorders. The 18 articles in this issue review advances in myeloid and lymphoid disorders in the context of the International Consensus Classification.

Acute lymphoblastic leukemia/lymphoma is now understood to be a genetically heterogenous disorder. The review by Duffield, Mullighan and Borowitz [6] highlights the rationale for the genetic subtypes, including new categories for precursor B, precursor T and early pre-T acute lymphoblastic leukemia. For precursor B neoplasms, the *BCR::ABL1* positive group is now divided into single (blast) and multilineage disease with the latter having similarities to blast transformation of chronic myeloid leukemia. Additionally, subcategories of the *BCR::ABL1*-like lymphoblastic neoplasms are now described. Many new genetic categories are introduced, such as early pre-T-ALL with *BCL11B* abnormalities. Some of the genetic changes included in the classification are not currently tested for routinely, but introduction of these biologic subtypes will hopefully initiate an increase in testing capabilities, as was as the case for the development of targeted therapies.

The reviews on acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) by Weinberg et al [7] and Hasserjian et al. [8] respectively, also expand genetic categories of these disorders, but also recognize the continuum between these disorders by introducing a new category of MDS/AML in adults without traditional de novo AML cytogenetics or mutation abnormalities.

While there are fewer changes in the myeloproliferative neoplasms and myelodysplastic/myeloproliferative neoplasms, Gianelli et al. [9] and Prakash et al. [10] respectively, highlight the refinement of disease criteria. The ICC retains accelerated phase as a category in chronic

myeloid leukemia and, in the setting of clonality, chronic myelomonocytic leukemia can now be diagnosed with lower peripheral blood monocyte counts.

Tzankov et al. [11] review the approach to eosinophilia and further characterize new genetic categories associated with tyrosine kinase abnormalities. Leguit et al. [12] review the criteria for mastocytosis including the clonal association between neoplastic mast cells and associated myeloid neoplasms.

Finally, pediatric and germline disorders are reviewed by Rudelius et al. [13] with expanded germline entities involving both myeloid and lymphoid neoplasms. The definition of juvenile myelomonocytic leukemia and related disorders are now separate from the myelodysplastic/myeloproliferative neoplasms.

For the lymphoid disorders, Sander et al. [14] review the diagnostic criteria and most recent information in chronic lymphocytic leukemia, B prolymphocytic leukemia, and mantle cell lymphoma including the spectrum from early lesions to aggressive transformed forms of these neoplasms. Novel genomic perspectives are updated with emphasis on alterations that may be of clinical interest in the near future. The spectrum of entities recognized under the term of "follicular lymphoma" (FL) has expanded in recent years, particularly with the identification of several entities that contrary to conventional FL do not carry the t(14,18). Laurent and colleagues [15] review issues related to grading FL, provide a comprehensive perspective of FLs negative for *BCL2* rearrangement, and highlight the relevance of molecular studies in the differential diagnosis of these entities and other related lymphomas.

The spectrum of plasma cell neoplasm is reviewed by Fend et al. [16] addressing the refinement in the diagnostic criteria and variants of lymphoplasmacytic lymphomas, monoclonal gammopathies of unknown significance, and solitary plasmacytomas. Primary cold agglutinin disease is now recognized as a distinct entity in the ICC and discussed in this review. The relevance of genomic studies is emphasized by the subdivision of multiple myeloma in different genetic groups in the ICC.

Aggressive B-cell lymphomas are examined in two articles. Song et al. [17] present the heterogeneous group of diffuse large B-cell lymphomas including new emerging entities. Recent genomic studies are changing our view of these neoplasms. Although still not considered ready for clinical use, they open new perspectives that most likely will influence our practice in the coming years. High-grade B-cell lymphomas are a challenging group of neoplasms thoroughly reviewed by King et al. [18] The paradigm of these tumors is the well characterized Burkitt lymphoma in which recent genomic studies are distinguishing EBV positive and negative tumors. The manuscript provides the rationale for the new definition of these tumors based on the presence of *MYC*, *BCL2*, and *BCL6* rearrangements and the new consideration of occasional TdT expression in these tumors.

The definition of classic Hodgkin lymphoma has not changed but the borders in the differential diagnosis with some diseases remains difficult. Tousseyn et al. [19] dissect these situations and provide insightful clues to identify the distinct entities. The article also addresses the rationale to change the historic term of "nodular lymphocyte predominant Hodgkin lymphoma" for the more biologically and clinically appropriate term of "nodular lymphocyte predominant B-cell lymphoma" included in the ICC. The change in the definition of gray zone lymphomas and the rational to restrict this term to "mediastinal gray zone lymphomas" is also presented in the light of recent genomic studies.

The presence of EBV in a lymphoproliferative disorder is always intriguing with epidemiological studies showing marked differences in geographical and ethnic distribution. Quintanilla-Martinez et al. [20] present a comprehensive view of all the B, T and NK lesions associated with this virus with new concepts, terminology and refinement of criteria proposed in the ICC. De Leval and colleagues [21] introduce the heterogeneous group of extranodal T and NK-cell lymphomas with lesions ranging from indolent to very aggressive behavior. As in other areas of the ICC, the new genomic information supports the characterization of these diseases and provides elements for refined diagnosis. Feldman et al. [22] address the predominantly nodal counterparts of T/NK-cell lymphomas. Lymphomas of T-follicular helper cell of origin are now recognized in the ICC as a single entity with three morphological variants sharing phenotypic and molecular features. Definitions of anaplastic large cell lymphoma and peripheral T cell lymphoma, NOS remain essentially unchanged but new subtypes are recognized based on genetic and gene expression profiles with impact in clinical behavior.

Goodlad et al. [23] address new advances in cutaneous lymphomas with the ICC segregation of primary cutaneous marginal zone lymphoma from MALT lymphomas. The term lymphoproliferative disorder is preferred over lymphoma for both this entity and primary cutaneous CD8-positive acral lesions. New biological insights illuminating the understanding of this group of diseases are also presented.

The goal of this special issue is to provide more details on the pathologic features of the entities of the International Consensus Classification of Myeloid and Lymphoid Neoplasms and to serve as a practical guide for diagnostic use of the classification. We thank all the participants of the Clinical Advisory Committee that helped develop the classification as well as the authors of this issue.

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