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Understanding the New WHO Classification of Lymphoid Malignancies: Why It's Important and How It Will Affect Practice

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Abstract

Improved delineation of lymphoid malignancy biology has prompted refinement of the 2008 World Health Organization (WHO) classification of hematopoietic and lymphoid tumors with a new framework introduced in 2016. This knowledge has provided valuable insights regarding management. Early clonal proliferations have been set apart given their limited potential for malignant dissemination. Increasing knowledge of molecular drivers of aggressive lymphomas has allowed subclassification and opportunity for clinical investigations to personalize therapy. New insights into T-cell pathophysiology has allowed grouping based on shared molecular and cellular features. This article will summarize the key changes in terms of diagnosis and histopathologic definitions, the impact of these changes on clinical management, and the challenges of future research in this field.

The Revised European American Lymphoma classification was based on the building of consensus, and it recognized that a comprehensive classification system was beyond the experience of any one individual.[1] The 19 members of the International Lymphoma Study Group contributed their diverse perspectives to achieve a unified point of view. In addition, the International Lymphoma Study Group made the decision to base its classification exclusively on published data; thus, for an entity to be included in the Revised European American Lymphoma classification, it had to be validated in more than one publication.

Recognition that the development of classification systems should be a cooperative effort was expanded with the third edition of the WHO classification.[2] It represented the first true worldwide consensus classification of hematologic malignancies and was the culmination of the efforts of a seven-member steering committee, 11 pathology committee chairs, 75 author contributors, and 44 clinician participants in a clinical advisory committee meeting.[3] In 2008, the fourth edition of the WHO classification involved the efforts of 138 authors and

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two clinical advisory committees comprising 62 clinical specialists with expertise in lymphoid and myeloid disorders.[4] The clinical advisory committee meetings were organized around a series of issues, including disease definitions, nomenclature, grading, and clinical relevance.[5] As with the third edition, the effort was coordinated by the European Association for Haematopathology and the Society for Hematopathology, led by the eight editors who served as a steering committee.

This model was maintained for the revision of the fourth edition, with a clinical advisory committee meeting held in 2014 to address newly emerging issues related to the definition of specific entities. The resultant revised fourth edition of the WHO classification was summarized in a review article published in *Blood* in 2016,[6] with publication of the complete monograph expected in the spring of 2017. It is being published as the revised fourth edition (not fifth edition) because fourth edition monographs for other organ systems are still in preparation, and preparation of a fifth edition must await the start of the next cycle.

The WHO classification embraces the principles of modern taxonomy by building a biomedical information network to promote disease discovery and pathogenetic insights, and to provide a framework for precision medicine.[7] The use of a common language internationally facilitates clinical trials and improves the standard of diagnosis and treatment in the general community. This article will highlight the revised classification and how it impacts clinical practice.

EARLY EVENTS IN LYMPHOID NEOPLASIA: BORDERLANDS OF MALIGNANCY

The multistep pathway of tumorigenesis is evident in the malignancies that develop in most organ systems. Additionally, histologic progression is a well-recognized feature of many lymphoid neoplasms, but the earliest events in lymphoid neoplasia are difficult to recognize. In fact, the lymphoid system historically has had no recognized “benign neoplasms,” a fact that may be related to the propensity of lymphoid cells to circulate and not remain confined to a single anatomic site.[8] The current WHO classification addresses the problem of clonal expansions of B cells or, less often, T cells that appear to have limited potential for histologic or clinical progression. The expanded knowledge of disease-specific genetic and phenotypic alterations has resulted in the detection of clonal lymphoid lesions sharing genetic and/or phenotypic aberrations with well-defined neoplasms such as chronic lymphocytic leukemia/ small lymphocytic lymphoma, multiple myeloma, follicular lymphoma (FL), and mantle cell lymphoma (MCL) without fulfilling diagnostic criteria for overt malignancy. These include monoclonal B-lymphocytosis (MBL), in situ follicular neoplasia, in situ mantle cell neoplasia, and monoclonal gammopathy of undetermined significance. Duodenal FL shares most phenotypic and genetic features with in situ follicular neoplasia, but interestingly also has some characteristics of extranodal marginal zone lymphoma.[9,10] New guidelines have been created for the diagnosis and management of these early lesions, which in general require no therapeutic intervention.

Some “indolent” and indeterminate clonal lymphoid proliferations appear to have a limited potential for progression, but they lack counterparts among the currently recognized subtypes of lymphoma. Some of these are of T-cell derivation and include indolent T-cell lymphoproliferative disorder of the gastrointestinal tract and primary cutaneous acral CD8-positive T-cell lymphoma, recognized as provisional entities in the revised WHO classification.[11,12] Pediatric-type FL falls into a similar category.[13,14] This clonal B-cell proliferation appears to have very limited capacity for aggressive clinical behavior, with little risk for progression following simple surgical excision of the affected node. However, its neoplastic nature is confirmed by the presence of clonal genetic alterations.[15–17] Recognition of these indeterminate clonal proliferations is important to avoid overtreatment of these patients. For example, some cases of pediatric-type FL might be incorrectly categorized as FL grade 3 A/B, resulting in inappropriate aggressive therapy.

Small B-Cell Neoplasms

Refinements have occurred in the understanding of small B-cell lymphomas. A long-standing problem had been the differential diagnosis of lymphoplasmacytic lymphoma and marginal zone lymphoma because both are usually associated with plasmacytic differentiation in the neoplastic cells. The identification of the *MYD88* L265P mutation in most cases of lymphoplasmacytic lymphoma, but only rarely in marginal zone lymphoma, has provided new tools for diagnosis.[18] The association of *MYD88* L265P and mutations in *CXCR4* has segregated immunoglobulin M monoclonal gammopathy of undetermined significance from other forms, placing it as closely related to lymphoplasmacytic lymphoma and Waldenstrom macroglobulinemia.[19–21]

MCL has been recognized as showing greater heterogeneity in clinical behavior and phenotype than previously appreciated. Leukemic non-nodal MCL has been delineated as a distinct variant associated with frequent splenomegaly, bone marrow and peripheral blood involvement, infrequent peripheral lymphadenopathy, and an indolent clinical course.[22,23] This variant is negative for SOX11, in contrast to classic MCL, and is usually derived from immunoglobulin heavy chain variable–mutated B cells. These cases had often been mistaken for chronic lymphocytic leukemia previously. SOX11 immunohistochemistry (IHC) has also proven to be useful in recognizing rare cases of classic MCL that are negative for cyclin D1.[24]

The basic approach to grading of FL remains unchanged. However, there is improved understanding of some FL variants, such as FL negative for CD10 (often positive for IRF4/MUM1) and cases of FL negative for t(14;18).[25] There have been new insights in the genetic heterogeneity of FL, with the possibility that analysis of the mutational profile will be incorporated in the future for assessment of clinical risk and protocol assignment.[26] Additionally, there is more formal recognition that FL grade 3B is biologically and clinically related to diffuse large B-cell lymphoma (DLBCL).[27]

Aggressive B-Cell Neoplasms

A major change in the classification of DLBCL is the recommendation that routine practice should recognize tumors belonging to the germinal center B-cell (GCB) and activated B-cell

(ABC) subsets using either IHC surrogates or other means, as they may become available.[6,28,29] This subdivision has proven prognostic value and also correlates with considerable differences in the molecular pathogenesis of the tumors. Recent studies also have shown that ABC compared with GCB lymphomas exhibit differential sensitivity to certain drugs, which may direct patient management in the near future.[30] Finally, it has become clear that most double-hit lymphomas (DHLs) fall within the GCB subgroup; thus, determination of cell of origin (COO) can facilitate identification of those tumors that should undergo fluorescence in situ hybridization for *MYC* rearrangement.[31]

The 2008 WHO classification included a borderline category termed "B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma (BL)," often referred to informally as "high-grade lymphoma unclassifiable" or HGLUC (Fig. 1). This group, admittedly heterogeneous, was used to designate high-grade B-cell neoplasms that had intermediate cytologic features between DLBCL and BL. Many cases diagnosed as HGLUC were so called DHL or more rarely triple-hit lymphoma, carrying translocations involving *MYC* and either or both *BCL2* and *BCL6*.[32,33] Moreover, clinical studies indicated that most of these DHLs were clinically aggressive with a poor outcome when treated with conventional chemotherapy, such as R-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). However, it also became apparent that DHLs were morphologically heterogeneous, such that some were diagnosed as DLBCL, whereas others, based on intermediate cytology, were classified as HGLUC.[34] The division of what appeared to be a genetically homogeneous group of tumors into two different diagnostic categories led to difficulties in evaluating this subgroup in clinical trials and evaluating current and evolving therapeutic regimens. Thus, the clinical advisory committee agreed on the creation of a unifying category designated as "high-grade B-cell lymphoma, with rearrangements of *MYC* and *BCL2* and/or *BCL6*." Notably, this category excludes cases of B-lymphoblastic lymphoma/ leukemia, which may be double hit as a consequence of progression from FL.[35–37]

Importantly, the WHO classification distinguishes between DHLs and tumors that have increased protein expression for BCL2 and MYC in the absence of dual translocations, often termed "double expressor" tumors. Double-expressor lymphomas are enriched in DLBCL of the ABC subtype of DL- BCL.[31,38,39] Dual expression of MYC and BCL2 is an adverse prognostic factor, but this may be based, at least in part, on factors related to the ABC designation.

There remains a small group of tumors that are perceived to be cytologically "high grade," perhaps requiring more aggressive therapy. These are designated as "high-grade, not otherwise specified (NOS)" and by definition exclude DHLs and BL. This designation should be used sparingly and is not simply based on a high proliferation fraction with Ki-67.[6] However, such cases may show overlapping features with BL.

The definition of BL is essentially unchanged in the revised classification. However, there is a rare variant of high-grade B-cell lymphoma that closely resembles BL but lacks the *MYC* translocation and instead has frequent aberrations involving the 11q region. These cases

occur mainly in children and are more often nodal than extranodal, in contrast to BL.[40] They are clinically aggressive but have a good response to therapy.

"Epstein-Barr virus (EBV)–positive DLBCL of the elderly" was a provisional entity in the 2008 WHO classification.[4] Since then, greater insight has been achieved regarding the epidemiology and prognostic significance of EBV in DLBCL. For one, the age distribution of EBV-positive DLBCL is much broader than originally thought and is not restricted based on age.[41,42] Interestingly, although EBV is an adverse prognostic factor in older patients, 43,44 younger patients appear to have a better prognosis.

The WHO classification newly recognizes EBV-positive mucocutaneous ulcer (EBV-MCU) as a localized lesion with a good prognosis and low risk of progression or dissemination. 45,46 EBV-MCU presents in patients with decreased immune surveillance for EBV, either related to advanced age or iatrogenic immunosuppression. The most common site of presentation is the oral cavity, including gingiva, but skin and intestinal mucosa also can be involved. Distinction from EBV-positive DLBCL is important because of very different treatment implications. Most patients with EBV-MCU can be treated conservatively.[47]

Peripheral T-Cell Lymphomas

There has been progress in illuminating the genetic landscape and classification of mature T-cell lymphomas. Genetic studies have shown recurrent mutations that affect a considerable proportion of cases of angioimmunoblastic T-cell lymphoma. Importantly, many of same genetic changes are observed in cases of peripheral T-cell lymphoma (PTCL) NOS that manifest a T follicular helper (TFH) phenotype.[48–50] For this designation, the neoplastic cells should express at least two or three TFH-related antigens among PD1, CD10, BCL6, CXCL13, ICOS, SAP, and CCR5. These observations have led to follicular T-cell lymphoma, angioimmunoblastic T-cell lymphoma, and nodal PTCL with a TFH phenotype being unified under a common heading.

Genomic approaches also have provided insights into the spectrum of CD30-expressing T-cell lymphomas and have facilitated the distinction of PTCL with high CD30 expression and ALK-negative anaplastic large cell lymphoma (ALCL), the latter having a superior prognosis.51 Studies have further elucidated the genetic complexity of ALK-negative ALCL, which is no longer a provisional category. Additionally, this genetic complexity provides important prognostic information; for example, cases of ALK-negative ALCL with DUSP22 translocation have an excellent prognosis, whereas cases with TP63 rearrangements have a very poor outcome.[52] Newly incorporated into the revised WHO classification is "breast implant–associated ALCL," which morphologically and phenotypically resembles other forms of ALCL but has very different clinical behavior. If neoplastic cells are confined to the seroma fluid surrounding the implant, patients can be managed conservatively with implant removal but no further therapy.[53]

Recent data also have led to changes in the categorization of intestinal T-cell lymphomas. It has become apparent that the two subtypes of enteropathy-associated T-cell lymphoma (EATL) are distinct, now clearly distinguished in the revised WHO classification. EATL, type I—now simply designated as "EATL"—is closely linked to celiac disease and is

primarily a disease of individuals of northern European origin. EATL, type II—now formally designated as “monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)”—shows no association with celiac disease and has an increased incidence in Asian and Hispanic populations.[54,55] There remains a small group of intestinal T-cell lymphomas that do not meet criteria for EATL or MEITL as currently defined. These should be designated as intestinal T-cell lymphoma NOS.

THE APPLICATION OF WHO CLASSIFICATION FOR LYMPHOID MALIGNANCIES ON CLINICAL PRACTICE

Here we will review the changes within the 2016 revision most pertinent to practicing hematologists and medical oncologists focusing on (1) the indolent B-cell and T-cell proliferations where early recognition is important given the opportunity to avoid aggressive therapy and (2) the aggressive lymphomas where risk factor identification is critical for accurate prognostication and for consideration of intensive therapy or focused clinical trials.

The new entities have critical implications for the treating physician (Table 1). Optimal diagnosis requires adequate tissue to accurately apply the classification. In most circumstances, a fine needle aspirate and even needle core biopsies are inadequate. When possible, consideration should be given to obtaining a surgical specimen. Furthermore, accurate staging remains essential for patient care. Bone marrow biopsy is still required for most of the non-Hodgkin lymphomas (NHLs), especially when confirmation of localized disease is warranted. These steps will facilitate an active conversation between the pathologist and treating physician, guiding subsequent management. Clinical applications of the new and modified entities are reviewed below.

Early Lymphoproliferative Disorders

B-cell and T-cell clonal expansions.—MBL is now understood to be the precursor to chronic lymphocytic leukemia, preceding the disease is most cases.[56] However, only a minority of patients with a peripheral blood B-cell clone will progress to an overt lymphoid malignancy. As such, the 2016 update now differentiates “low-count MBL” from “high-count MBL” with a peripheral blood clonal B-cell count of 0.5×10^9/L. Patients with high-count MBL require periodic evaluation given the genetic similarities to chronic lymphocytic leukemia and predisposition for progression over time.[57,58] Low-count MBL does not appear to have the same degree of B-cell receptor stereotypy or a similar potential for progression. As such, no specific follow-up is recommended for these patients at the current time.

In situ follicular neoplasia is used to describe a pattern of BCL2-overexpressing centrocytes and centroblasts in otherwise architecturally normal lymph nodes. A full staging work-up is needed to differentiate this entity from partial involvement by FL. In addition, larger biopsies are needed as flow cytometry of fine needle aspirations can be identical to FL because of similar cell surface markers.[11] Few patients appear to progress to disseminated FL.[59] As such, conservative management such as observation should be recommended in most cases.

Somewhat analogous to in situ follicular neoplasia, cyclin D1-positive B cells have been observed within the mantle zone of reactive lymphoid follicles.[60] The cells may be SOX11-positive and have been associated with other small B-cell lymphomas. Although uncommon, in situ mantle cell neoplasia also appears to behave in an indolent manner, rarely developing into overt lymphoma.[61]

Indolent T-cell proliferations have also been identified, warranting the addition of “indolent T-cell lymphoproliferative disorder of the gastrointestinal tract” and “primary cutaneous acral CD8-positive T-cell lymphoma” as provisional entities. Presenting within the gastrointestinal tract or the outer ear, respectively, these disorders can be mistaken for more aggressive T-cell lymphomas.[11,59] As such, identification is important to avoid overtreatment.

Small B-cell lymphoma variants.—FL remains incurable but with a median survival approaching 2 decades when presenting with grade 1 to 2 histology.[62] For patients with stage I disease, localized radiation has historically been recommend predominantly based on retrospective studies demonstrating tolerance of therapy and excellent long-term outcomes. 63 Analysis of the National LymphoCare database demonstrated wide variations in management, with chemoimmunotherapy being the most commonly used approach for patients with stage I disease.[60] The WHO classification now recognizes FL variants distinct from FL often presenting as an isolated lesion and having an excellent prognosis. Recognition is critical so that appropriate conservative management strategies can be used.

Despite the proliferative appearance, pediatric-type FL is most often localized and appears to behave in an indolent manner. It presents most often in children but can be diagnosed in young adults as well. A case series including 21 pediatric patients with stage I disease reported that when treated with excision only, none had progressed with a median follow-up of 57 months.[14] In addition, disease characterized by *BCL2* negativity and a proliferation index of greater than 30% predicted for similarly indolent behavior in adult patients presenting with stage I disease as well. As grade 3 conventional FL can present with a high proliferative index and lack of a *BCL2* rearrangement, discussion between the pathologist and treating physician is needed to differentiate high-grade FL from the pediatric-type disease.

Duodenal-type FL was originally named primary intestinal FL in the 2008 classification and was described as localized intestinal involvement, most often involving mucosa/submucosa in the second portion of the duodenum. Morphology, immunophenotype, and genetic features are similar to nodal FL. The lesions demonstrate indolent behavior, rarely progressing to nodal involvement and undergoing spontaneous regression in some cases.[9] As such, observation is the recommended management strategy for this entity as well.

The heterogeneous nature of MCL is well recognized, at times demonstrating relatively slow disease progression. For such cases, observation remains a reasonable management strategy. [61] Reports have suggested that the clinical phenotype of peripheral blood, bone marrow, and splenic involvement without lymphadenopathy may often demonstrate such indolent behavior. Two subtypes of MCL are now recognized in the 2016 update. Consistent with the

distinct clinical course, leukemic nonnodal MCL has a distinct pathogenesis, being SOX11-negative and having mutated immunoglobulin heavy chain variable region genes.[64] Although initial observation is appropriate for patients with this subtype, additional high-risk aberrations can be acquired resulting in a more aggressive clinical course.

EBV-positive MCU.—Differentiated from EBV-positive DLBCL, EBV-positive MCU is a provisional entity in the 2016 classification. Based on the viral pathogenesis, these lesions may present in elderly patients or in the setting of immunodeficiency.[45] Presenting as an ulcerative lesion of the skin, oropharynx, or gastrointestinal tract, these lesions have an indolent clinical course, typically not requiring systemic therapy. If clinically appropriate, reduction of immunosuppression can lead to regression.[43]

DLBCL and Other Aggressive B-Cell Neoplasms

Perhaps the WHO modifications affecting the largest number of patients with lymphoma are the changes for aggressive NHL subtypes. An improved understanding of DLBCL biologic heterogeneity has led to the identification of highly prognostic molecular markers and new drug targets, paving the way for clinical trials focused on disease subsets aiming to personalize therapy.

COO: GCB and ABC subgroups.—Following the identification of two distinct molecular subgroups reflective of COO, multiple groups have confirmed the biologic and prognostic differences of the GCB and ABC types of DLBCL.[62] As such, the 2008 WHO classification recognized these subsets of DLBCL. IHC emerged as a surrogate for gene expression as investigators attempted to extend COO determination to the clinic. The initially developed Hans algorithm used expression of CD10, BCL6, and IRF4/MUM1 to divide patients into GCB and non-GCB groups.[63] Eight subsequent algorithms attempted to improve the concordance with gene expression. Despite their limitations, the 2016 classification of “DLBCL NOS” now requires the identification of the COO subtype as determined by published ICH surrogates until gene-expression technology can be implemented in clinical practice.[65]

Clinical trials targeting COO.—Attempting to target the NF-kB signaling pathway, early-phase clinical trials demonstrated single-agent efficacy for targeted agents including bortezomib,[66] lenalidomide,[67] and ibrutinib,[68] predominantly in the ABC subset of DLBCL. After confirming safety in combination with R-CHOP, these early signals led to randomized studies evaluating the addition of the agents. Two randomized phase II studies evaluated R-CHOP with or without bortezomib in non-GCB DLBCL, replacing vincristine in the experimental arm of one trial.[69,70] No statistical difference in response rates, progression-free survival (PFS), or overall survival (OS) were observed between control and bortezomib arms in either trial. Ongoing randomized studies similarly evaluating the addition of lenalidomide or ibrutinib to R-CHOP are ongoing. Until these results are available, it would be premature to consider combining one of the agents with R-CHOP outside of a clinical trial. However, for patients without curative options or available clinical trials, single-agent lenalidomide may provide benefit in some patients with non-GCB DLBCL.[71]

These initial results give pause to how clinical trials are conducted in this population. The outcomes for the R-CHOP control arms appear better than expected, suggesting selection bias may be impacting the results. Rigorous inclusion criteria and the time needed to confirm COO may have led to the exclusion of patients with the most aggressive disease behavior, potentially explaining the low number of events observed in these studies. Additionally, relying on IHC may also limit the number of true patients with ABC included, reducing those most likely to benefit from a strategy targeting the NF-κB pathway. Future studies must streamline accrual and incorporate carefully written eligibility criteria so as to enroll the population intending to be studied. In the meantime, treating physicians must consider clinical trial options early in the disease course and understand limitations of the published literature so as to accurately counsel patients.

Double-hit lymphoma.—In addition to COO distinctions, alterations of *MYC* and those of *BCL2* and *BCL6* have clinical importance for large B-cell lymphomas. As described above, the prognostic significance of these aberrations has led to a new category in the WHO classification known as “high- grade B-cell lymphoma, with and without *MYC* and *BCL2* or *BCL6* translocations.” *MYC* rearrangements as detected by fluorescence in situ hybridization have been demonstrated in up to 15% of patients with large-cell lymphoma. An additional *BCL2* or *BCL6* translocation will be observed in a proportion of these patients, resulting in approximately 5% of patients with newly diagnosed DLBCL having double-hit genetics. The majority of reports have conferred a dismal prognosis for DHL after treatment with CHOP-based therapy.[72] The BC Cancer Agency reported a 5-year OS of 27% for those with concurrent *MYC* and *BCL2* translocations.[73] Subsequent retrospective series have described similarly poor outcomes, including a median OS of approximately 1.5 years.[72] This recognition not only has prompted the development of clinical trials focused on the high-risk subgroups but also may have immediate treatment implications.

Dose-intensive therapy for DHL.—Large retrospective analyses have suggested some benefit for using intensive induction regimens in DHL. A multicenter series of 311 patients with double-hit rearrangements reported an 8-month PFS for patients treated with R-CHOP compared with 22 months for those who received R-hyperCVAD, R-CODOX-M/IVAC, and DA-EPOCH-R.[74] Only in an exploratory analysis was a survival benefit suggested for patients with certain adverse prognostic factors. A second meta-analysis incorporating 394 patients from 11 retrospective studies compared outcomes for R-CHOP, DA-EPOCH-R, and R-hyperCVAD and again demonstrated a PFS advantage for the dose-intensive regimens without an OS difference.[75]

The only prospective data in this population has been reported in a preliminary analysis of a multicenter phase II trial evaluating DA-EPOCH-R in 52 patients with *MYC*-rearranged DLBCL and unclassified aggressive B-cell lymphoma.[76] Roughly half of patients tested also had a *BCL2* rearrangement. At median follow-up of 14 months, the PFS was 79% for the cohort and 87% for those with double-hit genetics. On the basis of this signal and the markedly inferior prognosis following R-CHOP, some investigators have advocated for first-line use of DA-EPOCH-R for patients with DHL.

Stem cell transplantation.—Retrospective series have also focused on outcomes following autologous stem cell transplantation for patients with DHL. As a whole, a survival benefit has not been appreciated with this consolidative strategy. One limitation is that patients with DHL exhibit high rates of early treatment failure. A subanalysis of the CORAL trial found that only half of patients with relapsed disease with a *MYC* rearrangement responded to salvage therapy resulting in a 4-year PFS of 18%.77 The SWOG-9704 trial suggested a PFS benefit for patients with high-intermediate and high risk International Prognostic Index scores.[78] However, further analysis demonstrated that none of the patients with DHL enrolled survived 6 months.[79] A retrospective analysis of post-transplant outcomes from two centers demonstrated that patients with DHL who are able to undergo autologous stem cell transplantation continue to have inferior outcomes with a 4-year OS of 25% compared with 70% for those without the aberrations.[80] Together, these results suggest that high-dose chemotherapy and autologous stem cell rescue does not overcome the high-risk biology of DHL. The incorporation of novel targeted agents with up-front treatment will ultimately be needed to better address the genetic complexity and refractory nature of this disease.

Double-expressor lymphoma.—As MYC and BCL2 can be activated through mechanisms other than translocation, several groups have evaluated protein overexpression. Compared with DHL, a larger proportion of patients overexpress MYC and BCL2, ranging from 20% to 44% of patients in retrospectively analyzed cohorts. Retrospective series have reported somewhat poor outcomes for this group of patients with an OS of 30% at 5 years following R-CHOP therapy.[38]

As with DHL, there is retrospective evidence that DAEPOCH-R may be able to overcome the poor prognosis associated with MYC and BCL2 overexpression.[81] However, 5-year outcomes for the randomized CALGB 50303 trial comparing R-CHOP and DA-EPOCH-R found no difference in PFS and OS in a large group of unselected patients with DLBCL.[82] Additionally, higher rates of febrile neutropenia, thrombocytopenia, and neuropathy were observed among those treated with DA-EPOCH-R. Given the available prospective data as well as the observation that patients with double-expressor large cell lymphoma do not uniformly have poor outcomes, the optimal treatment of this group is in the context of a clinical trial. Otherwise, R-CHOP remains the standard of care for this population at the current time.

Mature T-Cell Neoplasms

The progress made in identifying genetic drivers of PTCL has provided valuable insights into disease biology and new targets for study. However, most of this knowledge has yet to translate into the clinical arena. One exception is the CD30-positive T-cell lymphomas. Gene expression studies have demonstrated distinct profiles for the CD30-expressing PTCLs as compared with ALK-negative ALCL.[83] As such, ALK-negative ALCL has been moved from a provisional to a recognized entity in the 2016 update. The CD30 immunoconjugate brentuximab vedotin does appear to be active in PTCL.[84] Consistent with differences in disease biology, the responses in the relapsed/refractory setting, however, appear less frequent and less durable compared with ALCL.

THE IMPACT OF WHO CLASSIFICATION OF LYMPHOID MALIGNANCES ON CLINICAL TRIAL DEVELOPMENT

The previous two sections have outlined the key updates to the WHO classification of lymphoid malignancies based on new and increased emphasis on the role of biologic factors in the natural disease course and response to standard treatment. Although some of the shifts in classification are subtle, others are more overt, and they affect both the interpretation of existing literature and the design of studies moving forward. The two areas of clinical research most affected by these changes are aggressive B-cell lymphomas and mature T-cell lymphomas.

Aggressive B-Cell Lymphomas

There are four major changes in the classification of aggressive B-cell lymphomas, eloquently discussed above, that may affect clinical investigation: (1) the elimination of the category “B-cell lymphoma, unclassifiable, intermediate between DLBCL and BL” (also known as “BCLU” or “B-cell lymphoma, unclassifiable”), which was based on morphology; (2) the transition to combining these entities using shared genetic features of dual *MYC* and *BCL2* or *BCL6* rearrangements (double-hit/triple-hit lymphoma); (3) the requirement for COO testing in all aggressive B-cell lymphomas to distinguish GC and ABC DLBCL; and (4) the recognition of dual MYC and BCL2 protein overexpression (double-expressor lymphoma) as an adverse prognostic feature.

Although the clinical impact is clearly important, the newly recognized variants and prognostic features complicate the interpretation of existing trials. For example, the intergroup study CALGB 50303 was designed over a decade ago to compare standard R-CHOP with DA-EPOCH-R in treatment-naive DLBCL. With a primary endpoint of event-free survival (EFS), 524 patients were randomly assigned 1:1 to R-CHOP or DA-EPOCH-R. There was no difference in overall or complete response rate and no difference in the primary endpoint of EFS at either 3 or 5-year time points.[82] Similarly, the GOYA trial was designed to test the efficacy of the second-generation anti-CD20 obinutuzumab (G) compared with rituximab when added to a CHOP backbone.[85] GOYA was a large trial with 712 patients on R-CHOP and 706 patients on G-CHOP; again, there was no difference in the primary endpoint of PFS. On first glance, the conclusion from both these trials is that R-CHOP remains the standard of care for DLBCL. However, it is critical to acknowledge that there are a number of WHO-defined subsets mixed together in both of these trials, including some DHL, some double-expressor lymphoma, and of course the major dichotomy based on COO. Furthermore, many of these groups overlap; for example, the majority of DHL occurs in GC-DLBCL, whereas the majority of double-expressor lymphoma occurs in non-GC/ABC DLBCL.[38,86] Targeting what we currently consider one subset may be much more complex and thus confound the results of well-intentioned trials.

A second observation from ongoing trials is the surprisingly excellent outcome for patients treated with R-CHOP. For example, the CALGB 50303 statistical design was based on an assumed 55% EFS in the R-CHOP arm; surprisingly, patients receiving R-CHOP had an impressive 3-year EFS of 81% and 5-year EFS of 69%. The recently published PRELUDE

trial also found very few events in the R-CHOP arm followed by the placebo arm; this study tested the concept of postinduction consolidation with enzastaurin compared with placebo in patients with International Prognostic Index scores of 3 to 5.[87] There was no difference between the arms, and 4-year EFS was unexpectedly excellent at 70% in patients with highrisk disease.

Similarly, retrospective and large database reports suggest that ABC DLBCL via gene-expression profiling has an estimated PFS of 40% and OS of 50% to 60% following standard R-CHOP.[88] Similar reports using IHC-defined non-GC/ ABC phenotype show 2-year estimated PFS and OS of 28% and 46%, respectively.[89] By comparison, the outcomes for non-GC/ABC DLBCL on the standard R-CHOP arms of both the PYRAMID and German randomized phase II trials evaluating bortezomib in treatment-naive DLBCL showed 2-year PFS over 77% and OS 80% to 90% for this subgroup.[69,70] One explanation for discrepant outcomes between retrospective and prospective datasets is that the retrospective series includes all available patients, whereas prospective trials have inherent selection bias of only including patients fit enough to meet the trial inclusion criteria and with access to an academic center with the trial. The lesson here may be that, if we are to study high-risk and ill patients, there has to be a mechanism to enroll all patients in a more timely manner or to include flexibility regarding prephase therapy or even a full cycle of therapy while registration and regulatory processes proceed, pathology is being reviewed, biology is being confirmed, and logistics are settled.

The issues raised above make the need for adequate biopsy specimens, efficient diagnostics, and expert pathology review more imperative than ever. One lesson learned from ECOG 1412 is the need for timely and expert review. This trial is an important U.S. intergroup randomized phase II study prospectively testing the addition of lenalidomide to an R-CHOP backbone in DLBCL, with the hypothesis being that the immunomodulatory agent will overcome the negative prognosis of ABC-DLBCL (NCT01856192). Although the study has been actively accruing, an interim evaluation found an approximate 30% ineligibility rate based on central pathology review (personal communication, G. Nowakowski, Mayo Clinic). Given these findings, the protocol was amended to expedite central review; although the high rate of ineligibility persisted, and patients were identified in several business days instead of several months, facilitating targeted enrollment.

A related issue is the ability to define molecular subsets quickly and accurately. The original definition of GC compared with ABC subtype was based on gene-expression profiling in frozen specimens.[62] However, gene-expression profiling via the original assay is not commercially available, and frozen biopsies are not commonly performed. These limitations gave rise to a series of IHC algorithms that assign COO based on protein expression of CD10, MUM1, BCL6, and LMO2, among others.[90] The IHC panels are widely used and easily accessible, and the WHO 2016 classification allows these algorithms to be used for COO designation without specifying a preferred approach. Unfortunately, each of the IHC algorithms has an approximate 20% to 30% error rate when compared with the gold standard of gene-expression profiling. There can also be discrepancy among hematopathologists as to cases that are positive compared with negative for any given marker, leading to potential inconsistency for clinical trial purposes.

There are tools in development that might change this aspect of quickly defining aggressive B-cell lymphoma subsets. The assay that is furthest along uses NanoString technology and evaluates 20 genes (Lymph2Cx).[29] When compared with either the Hans or Choi IHC algorithms, Lymph2Cx was superior and much more aligned with the original gene-expression profiling. This assay is being used in a number of trials and touts a quick turnaround time from receipt of 36 hours. However, this rapid turnaround time does not include the time for biopsy specimens to be collected by the clinical trial center, reviewed locally, and then shipped to the company for analysis. These are just some of the logistic challenges that may hamper or delay biologic stratification in real time at study entry.

Overall, the new WHO update emphasizes that subsets in aggressive B-cell lymphomas exist and are likely to influence clinical trial design and interpretation. One suggested division for future trial design is to consider trials powered for the following groups: high-grade B-cell lymphoma with *MYC* and *BCL2* or *BCL6* rearrangements (independent of histology), DLBCL NOS with standardized assessment for COO and double-expressor phenotype, and DLBCL NOS without double-expressor or double-hit phenotype. These subsets are smaller than the overall population of DLBCL, and the need for community and academic centers alike to participate in large cooperative group trials or have a seamless referral process is critical if we are to move the bar higher for this disease with personalized therapy for each subtype of aggressive lymphoma.

Peripheral T-Cell Lymphoma

Outside of aggressive B-cell malignancies, the WHO update most significantly impacts the study of systemic aggressive T-cell lymphomas (T-NHL). PTCLs have historically been grouped by their main shared phenotype of T-cell derivation but are clinically and biologically distinct. Given their rarity, the overwhelming majority of trials lump all mature T-cell lymphomas together, often including the more indolent cutaneous T-cell lymphoma alongside aggressive systemic variants.

Analogous to the studies discussed above in DLBCL, pooling all mature T-NHL has likely led to the lack of data that moves the field forward significantly. One example is the continued use of CHOP for front-line therapy. Compared with B-cell histologies, CHOP has PFS rates of only 20% to 30% in T-NHL.[91,92] Attempts to improve on CHOP have taken several approaches: adding new agents to a CHOP backbone, consolidating with autologous stem cell transplantation, or using a non-CHOP regimen. Studies of a non-CHOP backbone are relatively uncommon and have been essentially single-arm, phase II, negative trials. The use of consolidative transplant (reviewed in Moskowitz et al[93]) improves outcomes for some patients, but ineligibility for transplant because of chemoresistance or comorbidities means this treatment is only applicable to the minority of patients. Building on CHOP despite the identification of rational targets has also proven to be difficult, with many trials failing to show a significant advantage to date.[94] There are several ongoing trials that are based on an integral marker (i.e., the use of brentuximab vedotin in CD30-positive malignancies) that may change this pattern, and results are eagerly awaited.

The identification of the TFH cell as the COO of angioimmunoblastic T-cell lymphoma and the subsequent recognition of a similar etiology in one-third of PTCL NOS is a new finding.

[95,96] As outlined in the first section, these T-NHL will now be grouped together under a common heading, which should facilitate clinical trials based on shared biology. Of note, angioimmunoblastic T-cell lymphoma and a number of related T-NHL appear highly dependent on epigenetic deregulation, which can and should be further studied with existing and emerging agents. For example, romidepsin is a histone deacetylase inhibitor already approved for relapsed/refractory T-NHL. Based on promising phase IB/II data,[97] there is an ongoing trial of CHOP with or without romidepsin (NCT01796002). However, this trial was designed prior to identification of the TFH phenotype and includes several histologies, possibly muting differences between the two arms. Similar to the discussion in DLBCL above, it will be necessary to power trials for subsets in the future.

CONCLUSION

The development of a universally accepted classification system has been of tremendous benefit to the field of hematologic malignancies. The 2016 WHO classification update of lymphoid malignancies includes several new entities and additional modifications that affect current treatment paradigms and provide a framework for future clinical trials. It is incumbent on treating physicians to understand the relevant changes. Doing so will facilitate dialogue with the pathologist so that an accurate diagnosis may be made, patients can be appropriately counseled, and state-of-the-art patient care can be delivered.

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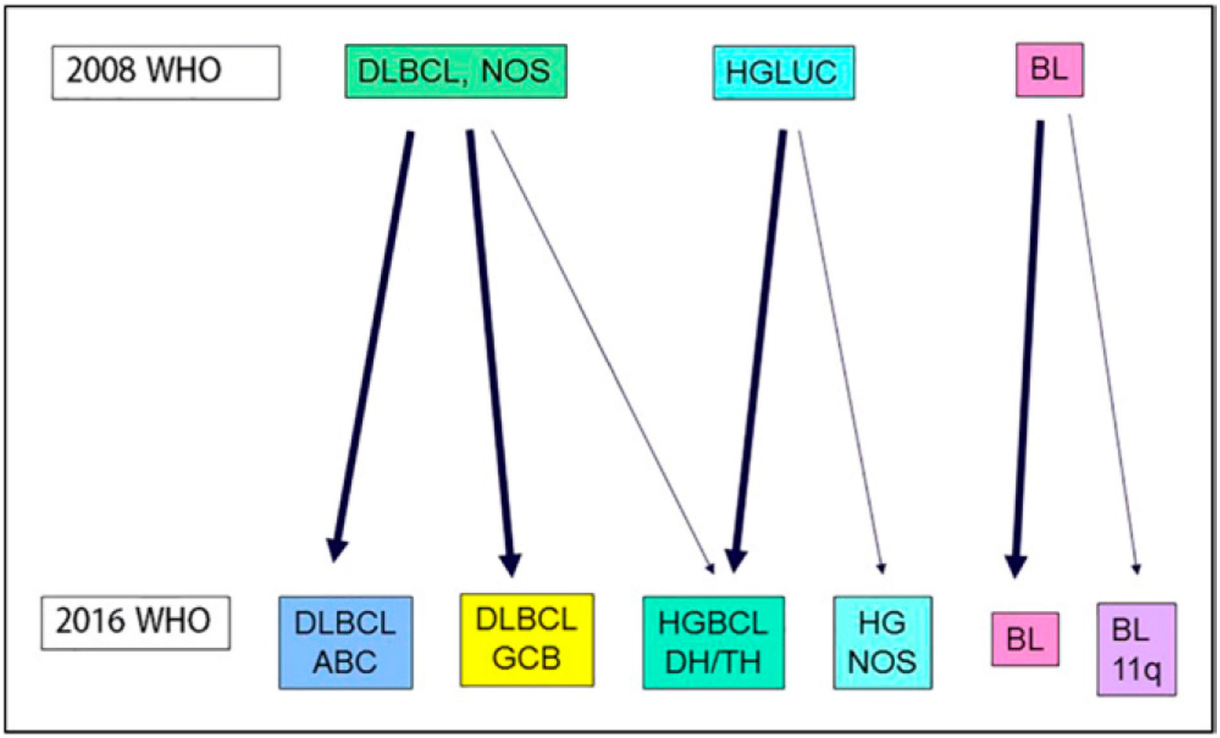
KEY POINTS

- The WHO Classification of Lymphoid Malignancies was updated in 2016, and there several key changes on pathologic and clinical perspectives.
- The updated guidelines provide an increased description of precursor and early lesions that may not need aggressive treatment.
- Patients with aggressive B-cell lymphomas are heterogeneous, and treatment is evolving.
- Clinical trials will need to focus on biologic lymphoma subtypes to move toward personalized therapy.



This diagram illustrates changes in the classification of diffuse large B-cell lymphomas (DLBCL), Burkitt lymphoma (BL), and high-grade B-cell lymphoma unclassified (HGLUC). DLBCL NOS is now further subclassified into the germinal center B-cell (GCB) and activated B-cell (ABC) subtypes. In addition, a small subset of DLBCL NOS with both *MYC* and *BCL2* and/or *BCL6* translocations are included in the category of high-grade B-cell lymphoma with double-hit (DH)/triple-hit (TH). Other cases in this category are derived from the 2008 category of HGLUC. The definition of BL is essentially unchanged, but there are rare BL-like lymphomas that lack MYC rearrangements and have aberrations at 11q. The density of the arrows indicates the relative frequency of cases reassigned to a different group.

FIGURE 1.
Navigating Changes in the Classification of Aggressive B-Cell Lymphomas, 2008 to 2016.

TABLE 1.

2016 WHO Classification Changes for B-Cell and T-Cell Neoplasms Affecting Clinical Practice*

Entity	Clinical Practice Implications
Monoclonal B-cell lymphocytosis	Distinguish low-count from high-count MBL
	Clinical follow-up not required for low-count MBL
In situ follicular neoplasiac	Low risk of progression to lymphoma
In situ mantle cell neoplasia	Low clinical risk
CD8+ T-cell proliferations	Conservative management
Pediatric-type follicular lymphoma	Conservative therapeutic approach; must differentiate from high-grade follicular lymphoma grade
Duodenal-type follicular lymphoma	Low risk of dissemination
EBV+ mucocutaneous ulcer	New entity associated with immunosuppression
Diffuse large B-cell lymphoma NOS	Distinction of GCB vs. ABC/non-GC type required
	Coexpression of MYC and BCL2 recognized as new prognostic marker
High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* translocations	New category for double and triple-hit lymphomas
	Consideration of dose-intensive therapy
ALK– anaplastic large cell lymphoma	Now a recognized entity; prognosis intermediate between ALK+ ALCL and PTCL

*Adapted from Swerdlow et al.[6]

Abbreviations: MBL, monoclonal B-cell lymphocytosis; NOS, not otherwise specified; GCB, germinal center B cell; ABC, activated B cell; GC, germinal center; ALCL, anaplastic large cell lymphoma; PTCL, peripheral T-cell lymphoma.

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