Editorial

Classification of Haematolymphoid Neoplasms: A work in progress towards more precise disease definitions in the era of precision oncology

Evidence-based disease classification is essential for optimal patient management and to further our understanding of disease causation and progression (aetiology and pathogenesis). It also allows us to understand disease epidemiology and develop prevention strategies. This has been the goal of the WHO Classification of Tumours, the classification system accepted worldwide. The WHO classification system has been the backbone for strategies of diagnosis and treatment of cancer, as well as research and education. The 'Blue Book' series, periodically updated and published by the International Agency for Research in Cancer (IARC), describes each tumour entity in great depth.

After several independent classification schemes for lymphoid neoplasms were being used in different parts of the world, lymphoma experts from around the world came together in 1994 under the auspices of the International Lymphoma Study Group to propose the Revised European–American Lymphoma (REAL) classification.[1] Subsequently, experts in myeloid and lymphoid neoplasms collaborated to develop the third edition of the WHO classification of haematolymphoid neoplasms in 2001. This classification has since been revised through the fourth and revised fourth editions, culminating in its current form, the fifth edition, published in its final form in 2024 (WHO-HEM5).[2,3] A recent review enumerates all the changes/revisions in the WHO-HEM5.[4]

Haematolymphoid neoplasms exemplify the current strategies of disease classification and utilization of disease biomarkers in cancer. In addition to histomorphological features, clinical presentation, immunophenotypic/immuno-histochemical features and genetic features (cytogenetic/molecular) contribute in an important manner to classifying and stratifying haematolymphoid malignancies. The reliance on genetic characteristics for cancer diagnosis has major implications for oncology practice across the world, as resources for genetic testing are not uniform. The WHO system addresses this challenge by establishing essential and desirable criteria for diagnosis, alongside category/family-level definitions in addition to entity-level definitions. This hierarchical structure organizes diseases in order of increasing levels of precision, wherein groups of multiple specific entities have been placed under an 'umbrella' family. Furthermore, a minimal number of diagnostic criteria required for a diagnosis have been enlisted to facilitate its application in regions of the world with limited resources.[2–5] The WHO classification system primarily classifies diseases based on the lineage of the presumed cell of origin. These lineages include myeloid, histiocytic, and dendritic, B cell, T cell, NK cell, and stroma-derived cells.

Morphology remains a key aspect of diagnosing haematolymphoid neoplasms. Disease classification is based on multiple parameters such as clinical presentation, clinical/imaging investigations and various laboratory tests. Immunohistochemistry, the preferred method for investigating antigen/protein expression in work-up of lymphomas and lymphoid leukaemias, can be complemented by flow cytometry, which can provide useful information in many situations, particularly for peripheral blood, bone marrow and body cavity fluid-based neoplasms. While morphology and immunophenotype are sufficient for diagnosing a major proportion of lymphoid neoplasms, association with infectious agents and genetic changes (chromosomal translocations, copy-number alterations, mutations and gene expression) play a major role in the diagnosis and classification of lymphoid proliferations and neoplasms.[4] In

contrast, the diagnosis of myeloid neoplasms is highly reliant on genetic studies for classification. Furthermore, flow cytometry plays a major role in the disease classification of myeloid neoplasms, and immunohistochemistry plays an important complementary role in bone marrow evaluations in myeloid neoplasms.

The changes to the WHO classification can be summarized as:

1. *Increasing number of entities defined by driver genetic abnormalities.* This includes a growing number of acute leukaemias.[2,6] In lymphomas, examples include Burkitt lymphoma, diffuse large B-cell lymphoma (DLBCL)/high-grade B-cell lymphoma (HGBCL) with *MYC* and *BCL2* rearrangements, and large B-cell lymphoma with *IRF4* rearrangement.[3,7]
2. *Improved understanding of how genetics and expression-based biomarkers impact disease stratification and patient management along the entire patient pathway*. For example, DLBCL not otherwise specified (NOS) constituting the largest entity among large B-cell lymphoma is heterogeneous in morphology, immunophenotype and genomics. While the germinal-centre B-cell subtype and the activated B-cell subtype remain relevant broad prognostic categories at disease presentation, genomic studies reveal multiple distinct clusters with differences in outcomes and molecular targets for treatment. These studies highlight the importance of in-depth genomic and transcriptomic analyses in lymphomas.[8–11] Patients of chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) are treated with Bruton Tyrosine Kinase (BTK) and BCL2 inhibitors. A proportion of patients of CLL/SLL harbouring mutations in *BTK* or *PLCG2* either at diagnosis or while on treatment do not respond to BTK inhibitors; mutations in *BCL2* have a similar impact on treatment with BCL2 inhibitors.[12,13] Assessing lymphoma samples for mutations will help guide patient management.
3. *Discontinuation of entities/terminologies that lacked a sound scientific basis.* WHO-HEM5 has removed B-prolymphocytic leukaemia (B-PLL) and hairy cell leukaemia variant (HCLv) due to a lack of distinct features in morphology, immunophenotype, biology and clinical outcome. A 'placeholder' termed 'splenic B-cell lymphoma/leukaemia with prominent nucleoli' (SBLPN) has been introduced for primary splenic lymphomas/leukaemias that cannot be definitively classified into distinct entities based on current knowledge.[3,7]
4. *Introduction of new entities*. Myelodysplastic neoplasm with biallelic *TP53* inactivation; myelodysplastic neoplasm, hypoplastic; acute myeloid leukaemia (AML) with *NUP98* rearrangement; myeloid/lymphoid neoplasm with *FLT3* rearrangement; cold agglutinin disease; monoclonal gammopathy of renal significance; and Epstein–Barr virus (EBV)-positive nodal T- and NK-cell lymphoma are some examples.[2–4]
5. *Grouping of entities with shared pathogenesis and other features*. Large B-cell lymphomas (LBCL) of immune-privileged sites is a new umbrella term introduced in WHO-HEM5. This term brings together a group of aggressive B-cell lymphomas that arise as primary tumours in the central nervous system (CNS), the vitreoretinal compartment, and the testes of immunocompetent patients, sharing similar biological features.[3,7] The WHO-HEM5 classification system uses a three-part naming scheme for lymphoproliferative disorders and lymphomas occurring in different settings of immune deficiency and dysregulation (IDD). This scheme incorporates the histological diagnosis, association with specific oncogenic viruses and the underlying immune dysfunction. The focus is on shared morphological characteristics and disease development mechanisms while acknowledging distinct aetiological agents. IDD conditions include those arising after solid organ or haematopoietic stem cell transplantation, human immunodeficiency virus (HIV) infection, immunosuppressive medications (including cancer chemotherapy), autoimmune diseases, many novel therapies, and inborn errors of immunity (primary immune deficiency states). These diseases range from hyperplasias to aggressive lymphomas.[14]
6. *Inclusion of neoplasms developing in individuals with germline abnormalities* such as ataxia telangiectasia (germline *ATM* gene mutations), Bloom syndrome (germline *BLM* gene mutations), RASopathies (germline RAS/MAPK pathway gene abnormalities) and Fanconi anaemia (germline FA/BRCA DNA repair pathway gene variants).[3,15]
7. *Inclusion of tumour-like lesions that have morphological or clinical overlap with neoplasms*. Examples include IgG4-related disease, different forms of Castleman

disease, Kikuchi–Fujimoto disease and autoimmune lymphoproliferative syndrome.[3,7,15]

Inevitably, the ongoing changes to the successive versions of the WHO classification have had an incremental reliance on genetic and expression-based diagnoses. Arriving at these diagnoses is technologically demanding and expensive. Even though the WHO classification considers these aspects, through providing a hierarchical structure and dividing diagnostic criteria into essential (the minimal required) and desirable categories, the usage of the classification may not be uniform across the world. However, it should be noted that the cost of sequencing is exponentially falling across the world, and expertise in newer technologies is exponentially improving in countries such as India. Additionally, having large case volumes brings economies of scale, hopefully making the required technologies affordable both in terms of costs and expertise. It also provides opportunities for countries such as India to forge ahead of the rest of the world.

Conflicts of interest. Kikkeri Naresh served as an expert member of the editorial board of the *WHO Classification of Tumours: Haematolymphoid Tumours*.

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