New paths through hematologic neoplasms

Karen Titus

March 2023—Updated classifications for hematologic neoplasms are here. Let the complications continue.

As with other specialties, hematopathology has been absorbing advances gleaned from molecular and genetic data. In some cases, this can tilt diagnosis away from primarily immunophenotypic approaches. It might lead to splits in what was formerly a single entity. On occasion, it might suggest further testing options that could be of value to patients now, or possibly at a date down the road.

Or it might just leave pathologists and their clinical colleagues peering at a lack of data, knowing they have to make decisions nonetheless.

Two groups—the World Health Organization and the International Consensus Classification—have put forth classifications to help physicians sort through the complexities.

The WHO published a beta version of the fifth edition of its Classification of Haematolymphoid Tumours in July 2022 (https://tumourclassification.iarc.who.int). Joseph Khoury, MD, the Stokes-Shackleford professor and chair of the Department of Pathology and Microbiology, University of Nebraska Medical Center, and chair of the CAP Cancer Committee, says he expects the final version of the WHO classification to be available this summer, when it will be published as another volume of the well-known Blue Books. In the meantime, the following papers delved into the intricacies of the classification:

- Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: myeloid and histiocytic/dendritic neoplasms. *Leukemia.* 2022;36[7]:1703–1719.
- Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: lymphoid neoplasms. *Leukemia.* 2022;36[7]:1720–1748.

The ICC published its classification of myeloid neoplasms, acute leukemias, and mature lymphoid neoplasms in September 2022 (https://bit.ly/ICC_09152022) in the following two papers:

- Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. *Blood.* 2022:140[11]:1200–1228.
- Campo E, Jaffe ES, Cook JR, et al. The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the clinical advisory committee. *Blood.* 2022;140[11]:1229–1253.

Classifications can sometimes feel as torturous—and perhaps as inscrutable—as a 16th-century sonnet. How best to encode complex matter into a universal format?

A new editorial governance structure was created to oversee the fifth edition of the WHO classification, namely, an editorial board that includes standing members—selected representatives from major medical and scientific organizations around the world—who oversee the entire series, in addition to expert members, selected for their expertise relevant to a particular volume. “Importantly, this allowed the selection of a multidisciplinary editorial team,” Dr. Khoury says, composed of pathologists, geneticists, oncologists, hematologists, and others, to produce the WHO Classification of Haematolymphoid Tumours. (Dr. Khoury is chair of the standing editorial board.) This governance structure abides by WHO rules of engagement (https://bit.ly/WHA69-10) and “permits a transparent process with appropriate checks and safeguards,” he says.

Dr. Joseph Khoury of the University of Nebraska Medical Center, at right, expects the final version of the fifth edition of the WHO Classification of Haematolymphoid Tumours to be published this summer. Two articles published last year in Leukemia provide official summaries of what the new classification entails. [Photo by: Jeff Barnes]

The ICC, says Daniel Arber, MD, the Donald West and Mary Elizabeth King professor of pathology and chair of the Department of Pathology, University of Chicago, used an approach that was similar to the one used in previous WHO editions of the classification; indeed, he notes, a number of authors on the ICC classification were involved with previous WHO classifications. Dr. Arber was the onsite organizer for the clinical advisory committee meeting and led the effort to develop the myeloid neoplasms and acute leukemias portion of the ICC classification.

Clinical input was key to developing both the WHO and the ICC classifications, say Dr. Khoury and Dr. Arber.

As the ICC developed its guideline, Dr. Arber says, the advisory committee served a key role. “The approach we took is to have pathologists come up with potential changes, based on new publications that might impact classification, and then have the clinicians comment on them.” An agreement from both pathologists and clinicians led to specific changes, he says.

“Particularly around genetics, there have been a lot of changes since the revised fourth edition of WHO,” from 2016, he says. “So the ICC incorporated those and moved more toward a molecular classification, particularly on the myeloid side.”

On the lymphoma side, Dr. Arber says, molecular aspects were also taken into consideration. He draws particular attention to follicular lymphoma types and T-cell follicular helper type lymphomas, calling them “still somewhat immunophenotypic driven but still informed by molecular studies.”

Dr. Arber is the lead author on the aforementioned *Blood* article that covers the myeloid and acute leukemia sections of the ICC classification.

Dr. Arber

The number of genetic categories has been expanded for the acute leukemias, he says, and the approach to acute myeloid leukemia with myelodysplasia-related changes adopts a more molecular approach.

In AML, he says, the list of cytogenetic abnormalities and gene mutations continues to grow, which has continued to be reflected in the classifications over the years. In some cases, it’s becoming more clear which mutations are drivers of disease.

“For acute lymphoblastic leukemia lymphoma,” he continues, “there are a lot of new genetic categories that have been discovered. People aren’t testing for them yet, but they are biologically relevant. So they are included in the classification with the hope that labs will start doing more testing for them.”

This is familiar territory for classifications, Dr. Arber says. Even if tests aren’t clinically available for mutations, drawing attention to them in classifications “helps drive labs to do this testing” when it becomes available, given their potential importance.

This approach does pay off, he adds. “It has helped lead to more targeted therapies for these patients.” And even when highly specialized testing is limited to only a few institutions—he cites testing for acute lymphocytic leukemia that is done at St. Jude Children’s Research Hospital as an example—“they identify subtypes that can be tested by other methods, such as FISH, which labs can adopt.”

More data has emerged in the area of chronic myelomonocytic leukemia, Dr. Arber says. The revised fourth edition of the WHO classification, he says, contains a category called CML-0 “defined by really low blast counts”—less than two percent blasts in blood and less than five percent blasts in bone marrow. Now, with more data available on this type of CMML, it appears that this classification isn’t as prognostically useful or as reproducible as was once thought, so the ICC classification eliminates this category.

Acute myeloid leukemias with mutated *CEPBA* is another area of change in the ICC classification. In the fourth edition of WHO, Dr. Arber says, any *CEPBA* mutation was seen as a good prognostic indicator. With additional data, he says, “Now it’s clear that the only thing that impacts prognosis is having an in-frame mutation in the bZIP region.”

The WHO classification, as noted, is in the beta version. “The value of the beta version is to provide a public input period while allowing the scientific and medical community to begin familiarizing itself with the new classification,” Dr. Khoury says. “This allows experts to provide feedback and any edits, comments, or corrections they might have.”

Nonetheless, the beta version is unlikely to change substantially, according to Dr. Khoury, who is the lead author on the aforementioned *Leukemia* article that details the section on myeloid and histiocytic/dendritic neoplasms. “The classification itself will not change,” he says. This edition marks the first time that the initial framework of the hematolymphoid classification was made available for public input early in the process, Dr. Khoury says. “It is a statement of inclusion, openness, and transparency. The availability of the beta version falls in the same line.” The fifth edition in its beta version is already being discussed at national and international meetings, he adds.

The classification builds on the work of prior classifications. One significant change overall is that it integrates advances in the molecular genetic characteristics used to classify cancers currently, Dr. Khoury says. “In addition, the fifth edition of the WHO hematolymphoid classification is now, for the first time, integrated into a broader hierarchical structure and a relational database that unifies the classification for all types of cancers recognized by the WHO.”

Moreover, he says, “It has included the multidisciplinary input of experts throughout the process, at the authorship level as well as at the editorial level.” This means the classification “is closely aligned with current clinical and pathology practices while being rooted in a cancer genetics foundation.”

“This was a huge effort,” says Dr. Khoury. The upcoming volume (it may be a two-volume set, he says) will be one of the largest in the series. “It’s about a thousand pages.” Though the material “could be the subject of a three-day conference,” he continues, the *Leukemia* papers provide the official summaries of what the new WHO classification entails.

Dr. Khoury notes additionally that the WHO authors streamlined the terminology used to name certain tumor types, consolidating advances in the field. They also adopted the most recent genetic nomenclature principles, those of the Human Genome Organization Gene Nomenclature Committee, and embedded them into the names of the various types of tumors as appropriate.

Other changes included expanding the number of entities that are diagnosed based on specific molecular alterations, Dr. Khoury says. “We also introduced, for the first time, placeholders that would allow for the introduction of genetically detected entities that we envision will be increasingly recognized in the next five years.”

Given the global impact and reach of the WHO, Dr. Khoury says, those who developed the WHO classification were mindful of making it applicable worldwide. The goal was to make it useful in places that might not have abundant resources, yet without compromising the science. “There are places in our own country that don’t have as many resources, in fact,” he says.

With two classifications available, pathologists might feel like they’re being forced to choose between two radically different choices—the difference between, say, the brisk theatrical release of *Once Upon a Time in America* and Sergio Leone’s make-yourself-comfortable director’s cut.

How should pathologists navigate differences that might occur between the two classifications? Says Dr. Khoury: “I think that’s one of the biggest areas of confusion in the community: people asking, ‘Do we use the WHO classification, or do we use the ICC?’ Which I find very unfortunate.”

Nobody benefits from a confusing situation, he continues. “Not the patients, not the providers, not the scientists.” To avoid confusion, Dr. Khoury recommends what he calls a “simple solution”: following the WHO classification. “It’s the standard that has underpinned the field for over two decades,” he says. “People propose classifications all the time, but when it comes to a standard-setting framework, the WHO classification should be it for all cancers.”

It’s worth remembering, as pathologists consider the two classifications, that they overlap by more than 90

percent, Dr. Khoury says. “There are areas of different opinion, but that’s where the data is just still lacking. And because they don’t have enough scientific data, they end up relying on consensus—and consensus can look different when different groups look at the same data.”

With that in mind, the best approach is to keep it simple, advise both Dr. Khoury and Dr. Arber.

Says Dr. Arber: “If the diagnosis is different in the two classifications, I think for a while people are just going to need to report that.” It’s similar to what happened with changes that occurred with the fourth edition of the WHO, he suggests. “Any time you change a classification, you have to explain what is in the prior classification to kind of bring people along, particularly clinicians.”

He provides one example from the ICC classification, which changed the name of nodular lymphocyte-predominant Hodgkin lymphoma to nodular lymphocyte-predominant B-cell lymphoma. “When I make the diagnosis of that disease now, I call it nodular lymphocyte-predominant B-cell lymphoma, and I’ll say, ‘ICC 2022,’ and in parentheses I add, ‘previously termed nodular lymphocyte-predominant Hodgkin lymphoma in the revised WHO fourth edition.’

“That’s what we did in the past when we had more than one classification,” Dr. Arber continues, “or when there was a change. Even as the WHO changed, you had to do that when there were changes between the classifications.”

Every institution will have its own approach. When there are differences, Dr. Khoury says, some laboratories may choose to present explanations when alternative viewpoints have been expressed, doing so in the comment portion of the report, but not the formal diagnostic line.

At UChicago Medicine, Dr. Arber says, “we continue to use the revised fourth edition WHO terminology, because that’s what everyone is most familiar with. If there are differences, we tend to use the ICC. But when the fifth edition WHO is finalized, we’ll also list that if there is a different diagnosis.”

He and his laboratory colleagues are discussing the changes with their clinical colleagues. “They’re familiar with what’s going on with the WHO and ICC classifications,” he says.

Other institutions have decided to use the WHO fifth edition, he says. Some are considering a hybrid approach, “which I don’t think is a great idea because I think that will create confusion.”

Nevertheless, he says, when there are differences between the WHO and ICC classifications, “I think you’ve got to use both to convey the differences.”

It’s possible an entity might be called one disease in one classification and a different disease in the other because of differences in criteria. “I’m hoping that’s not going to be a very common thing,” says Dr. Arber. If it does occur, “We’d just have to state, *That although we’re calling it disease X in the WHO, it would be disease Y in the ICC*, and then explain why. Then the clinician can decide.” He doesn’t think the differences will be a source of major treatment conundrums. “If it’s explained well, clinicians will understand.”

One area where a difference is likely to remain is on the myeloid side, Dr. Arber says. For patients who have 10 to 20 percent blasts, and who don’t have one of the recurring genetic abnormalities, the ICC adopted terminology to refer to these entities as MDS/AML, versus MDS-EB2 (excess blasts 2). The reason for this, he says: “Many of the clinicians wanted more flexibility in how to treat those patients.” The WHO classification has not adopted that approach, he notes. “Clinicians understand the blast counts, and they understand that these are equivalent between the two classifications, but it could cause confusion,” he says.

For physicians who practice in the community setting, any differences might seem onerous, at least at first, given that they’re treating so many different diseases, sans specialists. “They have a really hard job trying to keep up with every disease group they treat,” Dr. Arber says. “So the pathologist will have to help them in those settings. But I don’t think the terminology is so off the wall that it will be a huge problem. But the first time they encounter a diagnosis of MDS/AML, it may result in a conversation with the pathologist if they’re using that terminology.”

Dr. Arber hopes the two classifications will be quite close in their final forms. “Even now, they’re very close,” he says. “I’d say if the WHO keeps what they’ve proposed, there will be at least 90 percent overlap, if not more.” Which shouldn’t necessarily come as a surprise. “It’s two groups of people looking at the same literature—90 percent of the time they’re going to come to the same conclusions.”

For his part, Dr. Khoury says “the only obligation is to use the WHO classification,” noting the WHO is the global standard-setting organization for cancer classification and the basis for tumor registries, cancer epidemiology and surveillance, and third-party payers, for example. The WHO classification will also continue to be the standard for the CAP cancer protocols, he says, “including those for reporting hematolymphoid cancers.”

Karen Titus is CAP TODAY *contributing editor and co-managing editor.*