2016 WHO updates to the classification of hematologic neoplasms
Darshan Roy, MD
Assistant Professor
Department of Pathology
Director of Hematopathology
Rowan School of Osteopathic Medicine

Outline
• Myeloid neoplasms and acute leukemias
  • Myeloproliferative neoplasms (MPN)
  • Myelodysplastic syndromes (MDS)
  • MDS/MPN
  • Acute myeloid leukemia (AML)
  • Acute lymphoblastic leukemia (ALL)
• Lymphoid
  • Mature B‐cell lymphomas
  • Mature T and NK‐cell lymphomas
  • Hodgkin Lymphomas
Overview- reasons an update was necessary

1. Discovery of molecular features affecting diagnosis and prognosis
2. Improved characterization and standardization of morphological features aiding in the differentiation of disease groups
3. Evidence validating a clinicopathologic approach for classification

Myeloproliferative neoplasms

• Chronic myeloid leukemia (CML)
• Polycythemia vera (PV)
• Essential thrombocythemia (ET)
• Primary myelofibrosis (PMF)
• Chronic neutrophilic leukemia (CML)

• Mastocytosis has been removed from this category
Chronic myeloid leukemia (CML)

- Single relevant change in diagnosis of Accelerated Phase (AP)
  - Persistent or increasing WBC (>10x10^9/L) and/or persistent or increasing splenomegaly unresponsive to therapy
  - Persistent thrombocytosis (>100x10^9/L) uncontrolled by therapy
  - Persistent splenomegaly (>100x10^9/L) unrelated to therapy
  - Persistent cytogenetic evolution occurring after the initial diagnostic karyotype
  - 20% or more basophils in the peripheral blood
  - 10–19% myeloblasts in the blood or BM

- Provisional additions:
  - Evidence of Tyrosine kinase inhibitor (TKI) resistance
  - Hematologic resistance to first TKI
  - Evidence of resistance to 2 sequential TKIs
  - 2 or more mutations in BCR-ABL during TKI therapy

- Presence of fibrosis may indicate AP
- Presence of definitive lymphoblasts of any count should warrant concern for BP

MPN – Polycythemia vera (PV)

- PV (all 2 major criteria or first two 2 major + 1 minor)
  - Major criteria:
    - HGB (16.5 m, 16.0 f) or HCT (49% m, 48% f)
    - Bone marrow biopsy findings
    - JAK2 mutation
  - Minor criteria
    - Decreased serum EPO

- Criteria 2 not needed if sufficiently elevated HGB (>18.0 m, 16.5 f)
- However, the importance of bone marrow biopsy → evaluate fibrosis
MPN – Essential thrombocytemia (ET) and Primary myelofibrosis (PMF)

- Essentially unchanged.
- Discovery of recurrent CALR (calreticulin) mutation as diagnostic criteria of clonality in both ET and PMF (in addition to JAK2 and MPL)
- 20-25% of ET and PMF
- PMF if major clonal marker not identified, search for additional mutations (eg, ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1)

MPNs... the rest

- Chronic neutrophilic leukemia now has identifiable recurrent mutation, CSF3R mutations can be seen in 50-80% of patients
- Mastocytosis no longer considered MPN.

Myelodysplastic syndromes

Terminology “refractory anemia/pancytopenia” removed, now: “myelodysplastic syndrome with...”

- MDS with single lineage dysplasia
- MDS with ring sideroblasts (MDS-RS)
  - MDS-RS and single lineage dysplasia
  - MDS-RS and multilineage dysplasia
- MDS with multilineage dysplasia
- MDS with excess blasts
- MDS with isolated del(5q)
- MDS, unclassifiable
- Provisional entity: Refractory cytopenia of childhood
Myeloid – myelodysplastic syndromes

- Myeloid neoplasms with erythroid predominance (>50% erythroid cells)
- Now blast % of all nucleated cells (Previously counted blast % out of non-erythroid cells)
- Many cases of acute erythroid leukemia would now be classified as MDS-EB
- MDS defining genetic abnormalities must be identified by conventional karyotype (not by FISH alone)
- MDS with del(5q) may include 1 additional cytogenetic abnormality
  - As long as it isn’t monosomy 7 or del(7q)
- Clonal hematopoiesis of indeterminate potential (CHIP) - Somatic gene mutations can occur in low levels in normal patient populations
  - not solely sufficient for a diagnosis of MDS, however testing should be done in all new diagnosis to determine prognosis

MDS – Ringed sideroblasts

- SF3B1 gene identified and associated with ringed sideroblasts
  - If found, sideroblasts only need to account for 5% of nucleated erythrocytes (otherwise previous standard of 15%)
- MDS with ringed sideroblasts may now include multilineage dysplasia
New group – MDS with germline mutations

MDS/MPN

- Chronic myelomonocytic leukemia (CMML)
- Atypical chronic myeloid leukemia (aCML), BCR-ABL1
- Juvenile myelomonocytic leukemia (JMML)
- MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
- MDS/MPN, unclassifiable

MDS/MPN

- Chronic myelomonocytic leukemia (CMML)
  - Differentiate proliferative (WBC >13) vs dysplastic type
  - Now 3 categories based on blast percentage
  - CMML-0 (<2% peripheral blood, <5% bone marrow)
  - CMML-1 (2-4% peripheral blood, 5-9% bone marrow)
  - CMML-2 (5-19% peripheral blood, 10-19% bone marrow)
- Juvenile myelomonocytic leukemia (JMML)
  - ≥90% contain somatic or germline mutation in PTPN11, KRAS, NRAS, CBL, or NF1
- Refractory anemia with ring sideroblasts and thrombocytosis (RARS-T) is now MDS/MPN with ringed sideroblasts and thrombocytosis (MDS/MPN-RS-T)
Acute myeloid leukemia

- AML with recurrent genetic abnormalities
- AML with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- AML, NOS
- Myeloid sarcoma
- Myeloid proliferations related to Down syndrome

AML

- New provisional categories (both with worse prognosis)
  - AML with BCR-ABL1
  - AML with mutated RUNX1
  - CEBPA requires biallelic mutations
  - Acute erythroid leukemia (erythroid/myeloid type) removed
B-lymphoblastic leukemia/lymphoma (B-ALL)

Two new provisional categories:

- **B-ALL with intrachromosomal amplification of chromosome 21**
  - Occurs in 2% of pediatric ALL (usually older with lower WBC counts)
  - >5 copies of RUNX1 (or >3 copies on a single chromosome)
  - Poorer prognosis (partially overcome by aggressive therapy)

- **B-ALL, BCR-ABL1-like**
  - Involve other tyrosine kinases (over 30 different genes)
  - Cytokine receptor-like factor 2 (CRLF2)
    - Often associated with JAK2
    - Children with Down syndrome
T-cell lymphoblastic leukemia/lymphoma (T-ALL)

New provisional entity

• Early T-precursor (ETP) ALL
  • Retention of some myeloid and stem cell characteristics
  • CD1a-CD8-CD7+
  • Positive for one or more of the following: CD34, CD117, HLA-DR, CD13, CD33, CD11b, or CD65
  • Often have myeloid associated gene mutations (FLT3, NRAS/KRAS, etc) and lack T-ALL mutations (NOTCH1, etc).
  • Very poor prognosis

New provisional entity


Lymphoid neoplasms

- Mature B-cell neoplasms
- Mature T and NK neoplasms
- Hodgkin lymphoma
- Posttransplant lymphoproliferative disorders (PTLD)
- Histiocytic and dendritic cell neoplasms

Mature B-cell neoplasms

- Monoclonal B-cell lymphocytosis
  - Should be defined as low-count (PB CLL count of <0.5 x 10^9/L) vs high count
  - Low count rarely progresses to CLL
  - Non-CLL phenotype now recognized

- Chronic lymphocytic leukemia (CLL)
  - Now requires 5 x 10^9 PB CLL cells regardless of extramedullary disease

Mature B-cell neoplasms –Follicular lymphoma (FL)

- Follicular lymphoma
  - In situ follicular lymphoma renamed in situ follicular neoplasia (ISFN)
  - Pediatric FL renamed pediatric-type FL
  - No BCL2 (or BCL6 or MYC) rearrangements
  - Nodal disease with blastoid follicular centers
  - Localized (resection only)
  - Caution to avoid underdiagnosing Conventional grade 3 FL
  - Excluded by focal diffuse areas (DLBCL)
Follicular Lymphoma – continued

New provisional entity:
• Large B-cell lymphoma with IRF4 rearrangement
  • Young adults and children
  • Waldeyer ring/cervical lymph nodes
  • Low stage
  • Resemble FL grade 3B or DLBCL
  • MUM1 strongly expressed (usually with BCL6 and often with BCL2 and CD10)
  • High proliferative index
  • Lack BCL2 rearrangement
  • Must be distinguished from MUM1+ CD10- FL (older patients and associated with DLBCL)

Mature B-cell neoplasms - FL continued

• Follicular lymphoma – continued
  • Duodenal-type FL
    • Distinct from other GI FL
    • Resembles ISFN
    • May resemble MZL of MALT
    • Excellent outcome (some watch and wait)
  • Diffuse appearing FL
    • Inguinal masses
    • Lack BCL2 rearrangements
    • 1p36 deletion (not specific)
Mantle cell lymphoma (MCL)

- In situ MCL now in situ mantle cell neoplasia (ISMCN)
- Two indolent variants
  - Unmutated IGHV SOX11+ MCL
  - Nodal and may progress to "classic" MCL
  - Mutated IGHV SOX11- MCL
  - Frequently indolent leukemic variant
- Half of CCND1- MCL have CCND2 translocations
  - Usually IGK or IGL partner

Diffuse large B-cell lymphoma (DLBCL)

- Separation of germinal center (GC) and non-GC subgroups of DLBCL recommended
- MYC and BCL2/BCL6 expressor
  - IHC Expression vs rearrangement ("double/triple-hit" lymphoma now new category High Grade B-cell lymphoma)
  - >40% MYC, >50% BCL2 IHC positivity in tumor cells
  - Prognosis worse than NOS, better than double/triple hit
High Grade B-cell lymphoma (HGBL)

- **HGBL, NOS**
  - Includes previously described entity “B-cell lymphoma, unclassifiable with features intermediate between DLBCL and BL”

- **HGBL with MYC and BCL2 (or BCL6) rearrangements**
  - double/triple hit lymphomas
EBV+ DLBCL and EBV+ mucocutaneous ulcer

- EBV+ DLBCL, NOS
  - Previously included “of the elderly”
  - Worse prognosis than DLBCL, NOS

- EBV+ mucocutaneous ulcer, provisional entity
  - Self-limited disease, conservative management
  - Large Hodgkin-like cells
  - Patients with history of advanced age or iatrogenic immunosuppression

Burkitt lymphoma

- Provisional entity Burkitt-like lymphoma with 11q aberration
  - Similar to BL morphology and by gene expression profiling
  - Lack MYC rearrangement
Impact of molecular pathology on mature B-cell lymphomas

- Hairy Cell leukemia
  - Near 100% associations with BRAF V600E (not seen in HCL-v)

- Lymphoplasmocytic lymphoma
  - 90% have MYD88 L265P mutation
    - Not specific, seen in (IgM MGUS, DLBCL)
    - Not seen in myeloma

Mature T-cell and NK-cell neoplasms

- Follicular T-cell lymphoma
  - PTCL with follicular T-helper cell (TFH) phenotype (CD10+, PD1+, BCL6+) in a follicular pattern
  - May contain large EBV+ B-cells
  - Lack of high endothelial venules and expanded dendritic meshworks (of AITL)

- Nodal PTCL with TFH phenotype
  - Diffuse pattern but with follicular T-helper cell phenotype
ALK- Anaplastic large cell lymphoma

- No longer provisional entity
  - Require strong and diffuse CD30 positivity
  - Cohesive growth pattern with hallmark type cells
  - DUSP22 rearrangements have better prognosis (similar to ALK+)
  - TP63 rearrangements do much worse
- Breast implant associated ALK- ALCL
  - Provisional entity
  - 10 years after implant, associated with capsule seroma
  - Conservative management including excision

Representative cases of genetic subtypes of ALCL. (A) ALK-negative ALCL with DUSP22 rearrangement. The tumor cells are positive for CD30 and are negative for ALK, TIA-1, and p63. (B) ALK-negative ALCL with TP63 rearrangement. The tumor cells are positive for CD30, TIA-1, and p63 and are negative for ALK.
Enteropathy associated T-cell lymphoma (EATL)

- EATL only includes type 1
- Type 2 now defined as monomorphic epitheliotropic intestinal TCL (MEITL)
  - shows no association with celiac disease
  - increased in incidence in Asians and Hispanic populations

Hodgkin Lymphomas

- Nodular lymphocyte predominant Hodgkin lymphoma (NLP-HL) may evolve into T-cell histioocyte rich large B-cell lymphoma (THRLBCL)
  - THRLBCL-like transformation of NLP-HL
Conclusion

• Numerous recent advancements in genetic data (NGS) along with new treatment options drive the modifications to the WHO classification of hematopoietic neoplasms

END