Mature B-cell neoplasm (Overview)

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In this review article you will find information on the comprehensive differential diagnosis of mature B-cell neoplasms, which today is essential for classification, prognostic assessment and therapy planning.

Diagnostic Recommendation

Method	Anticoagulant	Recommendation
Cytomorphology	EDTA	mandatory
Immunophenotyping	EDTA or Heparin	mandatory
Chromosome analysis	Heparin	optional
FISH	EDTA or Heparin	mandatory
Molecular genetics	EDTA or Heparin	depending on the entity

General overview of mature B-cell neoplasms

The term mature B-cell neoplasms is used to describe biologically and clinically heterogeneous diseases of the B-lymphatic system. This includes the following entities, for which the MLL offers further information:

- Burkitt lymphoma (BL)
- Chronic Lymphocytic Leukemia (CLL)
- Diffuse large B-cell lymphoma (DLBCL)
- Follicular Lymphoma (FL)
- Hairy cell leukemia (HZL) and variant hairy cell leukemia (HZL-v)
- High grade B-cell lymphoma (HGBL) with gene rearrangements
- Lymphoplasmacytic Lymphoma (LPL)/Morbus Waldenström
- Mantle cell lymphoma (MCL)
- Marginal zone lymphoma (MZL)
- Monoclonal B-cell lymphocytosis (MBL)
- Plasma cell myeloma (PCM) & Monoclonal Gammopathy of undetermined Significance (MGUS)
- Prolymphocytic leukemia (B-PLL)

Definition and characteristics

Diseases of the lymphatic system of B-cells are characterized by a high heterogeneity. Depending on the entity, the clinical courses are indolent to aggressive. The different entities also differ in terms of genetics. For example, mature B-cell neoplasms exhibit a wide range of possible genetic abnormalities. Individual entities show typical patterns of balanced and/or unbalanced aberrations, but these are not specific enough for a final diagnosis. In the following overview, the characteristic immunophenotypic (see Table 1) and genetic features (see Table 2) of mature B-cell neoplasms are presented, which in combination with the methods of histology, immunohistochemistry and cytomorphology allow an exact diagnostic classification.

Classification

In the category of mature B-cell neoplasms, the WHO classification describes 34 different entities (Swerdlow et al. 2017), based on histology and immunophenotype. Cytogenetic and molecular genetic diagnostics significantly support differential diagnosis by detecting typical genetic patterns where appropriate. However, histology and immunophenotyping must always be consulted for an exact assignment of the disease to a specific entity.

Diagnostics

Diagnostics is based on the interaction of different methods:
- **Cytomorphology**: Assessment of the degree of maturity and infiltration in the bone marrow or peripheral blood.
- **Immunophenotyping:** assignment to the B or T cell lines. Many lymphomas show characteristic immunophenotypes (e.g. follicular lymphoma or mantle cell lymphoma), these are summarized in Table 1 (see Diagnostics, Immunophenotyping).
- **Chromosome analysis, FISH, molecular genetics**: Detection of characteristic genetic abnormalities, an overview is given in Table 2 (see Diagnostics, Chromosome analysis / FISH / Molecular genetics).
- **Immunohistochemistry:** central role in histopathology, especially of the lymph nodes.

Cytomorphology

Cytomorphology and histology are leading in the diagnosis of the different lymphoma entities for the control of the subsequent diagnostics. The assessment of the blood or bone marrow smear allows a first groundbreaking statement to be made as to whether lymphoma infiltration exists or is possible. Cytomorphology and histology are also necessary to assess the degree of lymphoma maturity.

Immunophenotyping

Besides CLL, other subtypes show characteristic immunophenotypes: Follicular lymphomas show a strong surface expression of immunoglobulins and mostly express the antigen CD10, whereas CD5 is not expressed. Mantle cell lymphomas express CD5 and are mostly negative for CD23 in contrast to B-CLL. Hairy cell leukemia expresses CD103, CD11c and CD25, whereas CD25 is not expressed in the variant form of hairy cell leukemia. Other lymphomas show less specific immunophenotypes, e.g. diffuse large B-cell lymphoma (DLBCL) or marginal zone lymphoma.

Table 1: Characteristic immunophenotypic findings in B-cell lymphomas

Antigene	B-CLL	B-PLL	MZL	SMZL	HZL	FL	MCL	DLBCL
CD19	+	+	+	+	+	+	+	+
CD20	(+)	+	+	+	+	+	+	+
CD22	(+)	+	+	+	+	+	+	+
CD23	+	-	-	-/+	-/+	+/-	-/+	+/-
CD25	-	-	-	-/+	+	-	-	
FMC7	-	+	+	+	+	+	+	+/-
CD79a	+	+	+	+	+	+	+	+
CD5	+	-	-	-	-/+	-	+	-
sIg	(+)	+	(+)	(+)/+	(+)	+	+	+/-
CD10	-	-	-	-/+	-/+	+/-	-/+	-/+
CD11c	-	-	+/-	-/+	+	-	-	

MZL: marginal zone lymphoma, SMZL: splenic marginal zone lymphoma, HZL: hairy cell leukemia, FL: follicular lymphoma, MCL: mantle cell lymphoma, DLBCL: diffuse large cell B-cell lymphoma

Chromosome analysis / FISH / Molecular genetics

Overview of cytogenetic abnormalities and molecular markers

In different entities of mature B-cell neoplasms, characteristic translocations occur which contribute to the pathogenesis. Often 14q32 is involved, whereby an oncogene gets close to the enhancer of the heavy chain of the immunoglobulin complex (IGH) and is overexpressed. More rarely, so-called variant translocations occur, in which instead of the IGH locus, one of the loci coding for one of the immunoglobulin light chains IGK (2p11) or IGL (22q11) is involved. Chromosomal analysis and interphase FISH analysis can be used to detect such characteristic rearrangements in B-cell lymphomas. Some of these (balanced) rearrangements, such as t(11;14)(q13;q32) or t(14;18)(q32;q21), can also be detected at the molecular level by PCR. However, since the break points at the genomic level can be very different, the hit rate of PCR is only 40-80%.

Table 2 provides a detailed overview of the genetics of the various mature B-cell neoplasms.

Table 2: Overview of cytogenetic and molecular changes in B cell neoplasms

Disease	Cytogenetic abnormalities	Molecular markers
BL Burkitt-lymphoma	**Balanced translocations:** t(8;14)(q24;q32)/IGH-*MYC*, t(2;8)(p11;q24)/IGK-*MYC*, t(8;22)(q24;q11)/IGL-*MYC* **Gains:** 1q, +7, +12 **Losses:** 6q, 13q32-34, 17p see also **BL**	*TCF3*, *CCDN3*, *TP53*, *RHOA*, *SMARCCA4*, *ARID1A*
CLL Chronic Lymphocytic leukemia	**Balanced translocations**: t(14;18)(q32;q21)/IGH/*BCL2* **Gains**: 12, 2p, 8q24 **Losses:** 13q, 11q, 6q, 17p, 14q see also **CLL**	*TP53*, *SF3B1*, *NOTCH1*, *ATM*, *BIRC3*, *POT1*, *MYD88*
DLBCL Diffuse large B-cell lymphoma	**Balanced translocations:** 3q27/*BCL6*, 8q24/*MYC* und 18q21/*BCL2* rearrangements: e.g.: t(14;18)(q32;q21) **Gains:** 3q, 9q see also DLBCL	*TP53*, *EZH2Y64*, *FOXO1*
FL Follicular lymphoma	**Balanced translocations:** t(14;18)(q32;q21)/IGH-*BCL2* rarely t(8;14)(q24;q32)/IGH-*MYC* or other 8q24/*MYC*-rearrangements, 3q27/*BCL6*-rearrangements **Gains:** 1(q), 6p, 7, 8, 12(q), 17, 18/18q, 21, X **Losses:** 1p, 6q, 7q, 9p, 10q, 13q, 17p see also FL	*BCL2*, *KMT2D*, *TNFRSF14*, *EZH2Y641*, *EPHa7*, *CREBBP*, *BCL6*, *MEF2B*, *EP300*, *TNFAIP3(A20)*, *FAS*, *TP53*
HZL und HZL-v Hairy cell leukemia and variant hairy cell leukemia	**HZL**: no specific abnormalities **HZL-v**: **-Gain**: 5 **- Losses:** 7q, 17p see also HZL	*BRAF* V600E (only for HZL) *TP53* (for HZL-v)
LPL Lymphoplasmacytic lymphoma	**Balanced translocation:** t(9;14)(p13;q32)/IGH-*PAX5* **Gains:** Trisomien 3, 4, 18 **Losses:** 6q (not specific for LPL) see also Morbus Waldenström	*MYD88* L265P, *CXCR4* S338X, *ARID1A*, *TP53*, *CD79B*, *KMT2D*
MCL Mantle cell lymphoma	**Balanced translocations:** t(11;14)(q13;q32)/IGH-*CCND1*, rarely: t(8;14)(q24;q32)/IGH-*MYC*, 3q27/*BCL6*-rearrangements **Gains:** 3q, 7p, 8q, 11q, 12, 13q, 15q, 18q, often tetraploid clones **Losses:** 1p, 6q, 8p, 9p, 11q, 13q, 17p, Y see also MCL	IGH-*CCND1*, *SOX11*, *UBR5*, *TP53*, *ATM*, *NOTCH1*, *NOTCH2*, *CCND1*-overexpression
PCM/MGUS Plasma cell myeloma/ monoklonal gammopathy of undetermined significance	**Balanced translocations:** t(4;14)(p16;q32), t(6;14)(p21;q32), t(11;14)(q13;q32), t(14;16)(q32;q23), t(14;20)(q32;q12), t(12;14)(p13;q32), 8q24/*MYC*-rearrangements **Gains:** 1q, 3, 5, 7, 9, 11, 15, 19, 21 **Losses:** 1p, 13 see also **MM**	*NRAS*, *KRAS*, *BRAF*
MALT Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue	**Balanced translocations:** t(11;18)(q21;q21), t(1;14)(p22;q32), t(14;18)(q32;q21), t(3;14)(p14.1;q32) **Gains:** 3, 18 **Losses:** 6q Frequencies of abnormalities vary depending on the location of the disease	-
nod. MZL Nodal marginal zone lymphoma	**Gains:** 3, 18 **Losses:** 6q	-
SMZL splenic mrginal zone lymphoma	**Balanced translocations:** complex cytogenetic abnormalities including t(9;14)(p13;q32) with *PAX5* and IGH-Gens **Gains:** 3(q), 12, 18 **Losses:** 6q, 8p, 7q, 13q, 17p	*NOTCH2*
B-PLL Prolymphocytic leukemia	17p13/*TP53*-Deletion, frequently complex karyotype, similar cytogenetic abnormalities as in CLL	*TP53*, *JAK1*, *JAK3*
HGBL High grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements	8q24/*MYC*-rearrangements together with 18q21/*BCL2*- and/or 3q27/*BCL6*-rearrangements. **Gains:** 1q, 3q, 7q, 8q, 12q, 18q **Losses:** 17p and 6q Exceptions are cases in which the criteria for follicular lymphoma or lymphoblastic lymphoma are met. In the past, these lymphomas were called "double hit lymphoma" or "triple hit lymphoma". These cases show a variable morphology of DLBCL, Burkitt lymphoma and rarely follicular lymphomas. see also **HGBL**	*TP53*, *MYC*

Prognosis

Due to the heterogeneity and complexity of the abnormalities, the prognostic significance in individual cases is highly variable within the different entities. Therefore, in addition to clinical parameters, many individual diagnostic findings are crucial for the correct timing between watch and wait and initiation of therapy. Increasingly, these findings also directly influence the choice of therapeutic agents (precision medicine) and are taken into account in the approval of drugs (e.g. TP53 alterations in CLL).

Recommendation

The diagnosis of mature B-cell neoplasms is currently much more comprehensive than 5 - 10 years ago and their results from blood, bone marrow and/or lymph nodes often have a direct impact on the choice of a potential therapy in addition to diagnostic and prognostic relevance. Various therapeutic approaches are so effective that today the determination of measurable residual disease (MRD) is partly introduced into remission controls. The method of choice here is usually immunophenotyping.

Important note on the test material
If lymphoma cells are detected in the peripheral blood, the diagnosis can initially be made with a high degree of certainty without a bone marrow biopsy or lymph node removal. Based on these findings, an extended material withdrawal is then advisable in individual cases and if clinically relevant.

References

Here you can find the corresponding references:
https://www.mll.com/en/diagnostic-offer/mature-b-cell-neoplasms/mature-b-cell-neoplasm-overview.html#references