High grade B-cell lymphoma (HGBL) with gene rearrangements

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Continuous research and targeted examinations of blood and bone marrow result in various diagnostic recommendations for patients with high grade B-cell lymphoma.

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	optional

Definition and characteristics of high grade b-cell lymphoma

Diffuse large B-cell lymphomas (DLBCL) show a *MYC* rearrangement in about 11%, of which 39% show an additional BCL2, 15% a *BCL6* rearrangement and 12% both rearrangements (Rosenwald et al. 2019) and are classified as high grade B-cell lymphomas with *MYC* and *BCL2* and/or *BCL6* rearrangements (HGBL). In about 20% of the cases, they are caused by transformation from follicular lymphoma.

Compared to DLBCL, high grade b-cell lymphoma (HGBL) more often present with high stage, extranodal and/or CNS involvement, B-symptoms, raised white cell count or increased LDH at initial diagnosis (Davis 2019).

Classification of high grade b-cell lymphoma

The term high grade b-cell lymphoma (HGBL) was newly introduced in the WHO classification 2017 (Swerdlow et al. 2017). A distinction is made between two categories:

1. High Grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements. With the exception of a few follicular or B-lymphoblastic lymphomas with these aberrations, these are lymphomas with an 8q24/*MYC* rearrangement in combination with a 18q21/*BCL2* and/or a 3q27/*BCL6* rearrangement.
2. High Grade B-cell lymphoma not otherwise specified (HGBL, NOS) encompasses cases with no *MYC* and *BCL2* and/or *BCL6* rearrangements. They have features intermediate between DLBCL and Burkitt lymphoma (BL) or appear blastoid, but histologically they cannot be clearly assigned to a diffuse large cell lymphoma.

In the past these lymphomas were called "double-hit lymphomas" or "triple-hit lymphomas". These cases show a variable morphology of DLBCL, Burkitt lymphoma and rarely follicular lymphomas.

The term BCLU lymphoma (B-cell lymphoma, unclassifiable), which was introduced in the WHO classification in 2008 and which included the majority of cases that now belong to the category of high grade b-cell lymphomas, is no longer recommended according to the WHO classification in 2017 (Swerdlow et al. 2008, Swerdlow et al. 2017). Rarely have "quadruple hit lymphomas" (= multiple hit lymphomas) been described in which a *CCND1* rearrangement is also found in addition to *MYC/BCL2/BCL6* (Haberl et al. 2016). However, these are not included in the WHO classification 2017.

High grade b-cell lymphoma -Diagnostics

Cytomorphology

The cytomorphology is a guiding principle for the control of the downstream diagnostics. For example, the assessment of the bone marrow smear provides an initial groundbreaking statement as to whether lymphoma infiltration exists or is possible. Cytomorphology and histology are also useful for assessing the degree of lymphoma maturity.

"Double hit" high grade b-cell lymphoma show a very variable morphology. The majority (69% for *MYC/BCL2* and 85% for *MYC/BCL6*) have a DLBCL morphology (Li et al. 2016). In contrast, the morphology of HGBL-NOS is more similar to Burkitt's lymphoma with a partly very monomorphic population, but less strongly basophilic cytoplasm and mostly lacking vacuoles.

Immunophenotyping

High grade b-cell lymphomas are mature B-cell lymphomas with expression of CD19, CD20, CD79a and PAX5 and lack of TdT. Some double-hit HGBL cases lack surface immunoglobulin expression as detected by flow cytometry, possibly due to multiple translocations in the IG locus. The absence of IG expression should not be interpreted as proof of a precursor B-cell phenotype. CD10 and BCL6 expression is found in most of these lymphomas (75-90%), and IRF4/MUM1 is expressed in approximately 20% of the cases.

Chromosome analysis

Cytogenetically the high grade b-cell lymphoma (HGBL) - besides the defining *MYC*, *BCL2* or *BCL6* rearrangements - usually show a complex karyotype with numerous numerical and structural aberrations. Frequent cytogenetic alterations include gains of chromosomal segments 1q, 3q, 7q, 8q, 12q, 18q and losses of 17p and 6q.

FISH

In high grade b-cell lymphoma (HGBL), FISH is well suited to address the gene loci known to be affected in interphase cell nuclei. In addition, FISH can clarify and back up the results in complicated chromosomal alterations in addition to the classical metaphase analysis by means of painting or 24- colour FISH.

Molecular genetics

Molecular genetic mutations were observed in the genes *TP53* (21%) and *MYC* (24%) (Haberl et al. 2016). *TP53* mutations were more frequent in *MYC/BCL2* rearranged high grade b-cell lymphomas than in those with *MYC/BCL6* rearrangement (Gebauer et al. 2015). MYD88 mutation was rarely found. *TCF3* mutations or the ID3 deletion are more common in Burkitt lymphoma.

HGBL-NOS by definition do not have a combined *MYC* and *BCL2/BCL6* rearrangement, about 20-35% show a single MYC rearrangement.

High grade b-cell lymphoma: Prognosis

High grade b-cell lymphoma is mostly an aggressive lymphoma with an adverse prognosis, because the *BCL2* and/or *BCL6* additional rearrangements are an independent, negative prognostic factor for survival in the first two years. There is no prognostic difference between "double hit" (*MYC/BCL2* or *MYC/BCL6*) and "triple hit" (*MYC/BCL2/BCL6*) HGBL. In contrast, the *MYC* rearrangement partner plays a role, since the negative effect could only be shown in a *MYC*-IG rearrangement and in a non-IG *MYC* rearrangement the survival corresponds to that of classical DLBCL and/or DLBCL with sole *MYC* rearrangement (Rosenwald et al. 2019). In addition, patients with a morphology similar to DLBCL seem to have a better prognosis than patients with a Burkitt-like morphology.

More intensive therapies (e.g. with EPOCH-R) lead to a longer progression-free survival (Petrich et al. 2014, Dunleavy el al. 2014). Due to the high proportion of CNS involvement of up to 45%, CNS prophylaxis should also be considered (Friedberg 2017). A further improvement of the prognosis could be achieved by using specific therapies such as BCL2 inhibitors or inhibitors of the bromodomain and extra-terminal protein family (BET inhibitors). The use of anti-CD19 CAR-T cells at an early stage such as the first relapse could also further improve the prognosis (Wang et al. 2020).

Recommendation for high grade b-cell lymphoma

Important notes on the test material
If enlarged lymph accounts are clinically in the foreground, one of them should be removed and processed histologically and immunohistologically. Since an infestation of the bone marrow occurs frequently (59-94%), the diagnosis can often be made in the bone marrow. In addition, a CSF examination by immunophenotyping is recommended. It should be noted that the cerebrospinal fluid should be examined within four hours on the same day if possible in order to obtain valid results. If such a quick shipment is not possible, TransFix® tubes containing an agent that stabilizes the surface antigens for about 72 hours can be shipped.

References

You can find the corresponding references here:
https://www.mll.com/en/diagnostic-offer/mature-b-cell-neoplasms/high-grade-b-cell-lymphoma-hgbl-with-gene-rearrangements.html#references