

Cytogenetic and molecular testing in lymphoma patients

Part 2: Aberrations in aggressive B-cell lymphomas, Hodgkin lymphoma, and T and NK lymphomas

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On behalf of the BHS Lymphoproliferative Disease Committee 2017:

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SUMMARY

It is now well demonstrated that cytogenetic and molecular testing are valuable tools for the diagnostic, prognostication and decision of treatment strategy in lymphoproliferative disorders. This study gives an overview of the genetic tests that represent current and future clinical assessment tools in the context of lymphoid malignancies. This review has been divided into two distinct but complementary parts. The already published part 1 addressed the genetic aspects of low grade B-cell lymphomas and very briefly described the different technical methods that can be used in routine practice for the clinical management of lymphoid malignancies. This second part covers aggressive B- and T/NK-cell lymphomas as well as Hodgkin lymphoma.

(BELG J HEMATOL 2018;9(7):266-78)

INTRODUCTION

Cytogenetic and molecular testing play a major role for the diagnostic and prognostic assessment in lymphomas as well as for selection of therapeutic strategies. According to the 2008 and the more recent 2016 revision of the World Health Organization (WHO) classification of lymphoid neoplasms, genetic markers are as important as clinical, morphologic and immunophenotypic features to define some unique entities.¹

The first part of the review was devoted to the mature B-cell lymphomas. This second part covers the genetic aspects of aggressive B- and T-cell lymphoma and of Hodgkin lymphoma.

As for the first part, different tables classifying the use of genetic markers (cytogenetic and molecular) in three categories according to evidence-based medicine criteria are proposed:

- mandatory: the test has demonstrated its clinical utility and is needed for the clinical management of the patient (diagnosis, prognosis, predictive value and/or theranostics);
- optional or recommended: although the test has demonstrated its clinical significance, it is not mandatory for diagnosis or choosing frontline treatment nowadays;
- under development: the test needs further clinical assessment to demonstrate its clinical significance and utility.

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Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.

Keywords: aggressive B-cell lymphoma, cytogenetics, Hodgkin lymphoma, lymphoblastic lymphoma, molecular testing, T/NK lymphoma.

CYTOGENETIC AND MOLECULAR MARKERS IN AGGRESSIVE B-CELL LYMPHOMA

The two main entities of aggressive B-cell lymphomas are Burkitt lymphoma (BL) and diffuse large B-Cell lymphoma (DLBCL). The characterisation of borderline entities has been debated for decades. Currently, there is no biologic marker capable of distinguishing them from DLBCL or BL. However, the distinction is crucial because of the radically different therapeutic approach for each of these lymphomas and the very unfavourable prognosis of aggressive B-cell lymphomas, especially in adult patients. The discrimination between these three entities is therefore based on a bundle of arguments, of which the cytogenetic approach is an integral part.

BURKITT LYMPHOMA

BL is characterised by a recurrent translocation involving the *MYC* locus/8q24 to one of the three immunoglobulin loci, predominantly the heavy chain (*IGH*) locus at the chromosome region 14q32 or the light chain lambda (*IGL*) at 22q11 and, less frequently, the kappa (*IGK*) locus at 2p12. In sporadic and immunodeficiency-related BL, most breakpoints are close to or within *MYC*, whereas in endemic cases most breakpoints are dispersed over several hundred kilobases (Kb) further upstream of the gene. Due to these translocations, control of normal *MYC* gene expression is lost, leading to the constitutive expression of *MYC* protein.² The *IG-MYC* rearrangement represents the primary cytogenetic abnormality of BL. However, the major difficulty is that the *MYC* rearrangement is not specific of BL and is also encountered in other aggressive B-cell lymphomas where the gene partner may be a non-immunoglobulin gene, and the *MYC* alteration may be associated with *BCL2* (18q21) and/or *BCL6* (3q27) rearrangements. In this context, the cytogenetic diagnostic approach of aggressive B-cell lymphomas is based on the following elements: complexity of the karyotype, presence (or not) of rearrangements of *MYC* and/or *BCL2* and/or *BCL6* genes and even involvement of the *IGH*, *IGK* or *IGL*.

Although the karyotype of BL is usually simple (≤ 3 chromosomal aberrations), additional chromosomal abnormalities are reported in 30% of cases and may influence disease progression. The 1q gain (by duplication, unbalanced translocation or isochromosome 1q) constitutes the most frequent secondary anomaly (40-50%). Chromosome 13q changes (addition, deletion or complex intrachromosomal rearrangement) are detected in 30% of cases. Partial or total gain of chromosome 7 (+7q/+7) is seen in 10% of cases, trisomy 12 in 5%, 6q deletions in 5% and more rarely 17p deletion

in 3%. Some of these aberrations (13q abnormalities and complex karyotypes) have been shown to be independently associated with reduced survival. *BCL2* and *BCL6* are never rearranged in BL.²⁻⁵ Two pivotal studies have demonstrated a specific gene expression profile (GEP) that may distinguish BL from other aggressive mature B-cell lymphomas with *MYC* rearrangement.^{6,7}

MYC overexpression alone is not sufficient to trigger BL lymphomagenesis. Recent next-generation sequencing (NGS) studies of BL have improved our understanding of the pathogenesis of this lymphoma.⁸⁻¹⁰ Mutations in the transcription factor *TCF3* or its negative regulator *ID3* occur in about 70% of sporadic and immunodeficiency-related BL and in 40% of endemic BL. *TCF3* promotes survival and proliferation in lymphoid cells by activating the B-cell receptor (BCR)/phosphatidylinositol 3-kinase (PI3K) signalling pathways and modulating the expression of *CCND3*, a D-type cyclin that regulates G1-S cell-cycle transition. *CCND3* itself can also be mutated in BL (30%), contributing to its highly proliferative phenotype.^{8,11,12}

BURKITT-LIKE LYMPHOMA WITH 11Q ABERRATION

This new provisional entity closely resembles BL but lacks *MYC* rearrangement and is characterised by an interstitial 11q23 gain immediately followed by a telomeric loss at 11q23.^{2,13} Up to 10% of cases with the clinical, morphologic and immunophenotypic features of BL lack a demonstrable *MYC* translocation by fluorescent in situ hybridisation (FISH).³ Caution is warranted before concluding that these are indeed true *MYC*-negative BL, because the scattering of breakpoints in the *MYC* and immunoglobulin loci, along with small insertions of one locus into the other, can render *MYC* breaks undetectable even if an extensive set of FISH probes are applied (both break-apart and fusion probes for t(8;14)(q24;q32), as well as *IGH*, *IGL* and *IGK* break-apart probes). The detection of the 11q aberration relies on molecular karyotyping rather than karyotype (cryptic) and FISH (heterogeneous breakpoints). Because this 11q aberration is also detected in *MYC* rearranged high grade lymphoma, it cannot be considered as a surrogate for *MYC*-induced lymphomagenesis.¹⁴ However, additional studies are needed to better understand such lymphoma whose clinical course seems to be similar to classical BL.

DIFFUSE B-CELL LYMPHOMA

No specific genomic aberrations are known for DLBCL. The karyotype of DLBCL is most often complex, hyperdiploid in two third of the cases, with an increased frequency of X, 3, 5, 7, 11, 12 and 18 chromosome gains (10-15%

of cases). Losses and deletions are related to chromosomes Y, 4, 6 and 15 (5 to 10% of cases). The 14q32/*IGH* rearrangements constitute the most frequent structural anomaly (40-50% of the cases). The *BCL6* gene is rearranged in 30-40% of cases, most often in the form of a translocation t(3;14)(q27;q32) *IGH-BCL6*, although more than 20 *BCL6* partner genes were identified in the DLBCLs (*IKZF1*, *MYC*, *CIITA*, *PIM1*, *RHOH*, etc.). Rearrangement of *BCL2* is observed in 15-20% of cases, frequently by translocation t(14;18)(q32;q21) *IGH-BCL2*. Rearrangement of *MYC* in DLBCL is observed in ~5% of cases of adult DLBCL and 15-25% of paediatric DLBCL. *MYC-IG* or *MYC-non IG* rearrangements are reported, involving various *MYC* partners (*BCL6*, *PAX5*, *BCL11A*, *IKZF1* for the most frequent).¹⁵

The transcriptomic studies allowed the identification of several molecular subtypes of B lymphomas, defined by their physiological cell counterpart: germinal centre B-cell-like (GCB), activated B-cell-like (ABC) and primary mediastinal B-cell lymphoma (PMBL). Various immunohistochemical (IHC) algorithms rely on these transcriptomic data that are widely used routinely. They are based on the expression of a selection of cell markers, in particular CD10, *BCL6* and *MUM1* for the Hans algorithm, the most frequently used. It allows discriminating the subtype GCB from the non-GCB subtype of DLBCL.¹⁶ The clinical relevance of this distinction is based on the less favourable prognosis of non-GCB DLBCL. The translocation t(14;18) *IGH-BCL2* and the gains 2p, 12q, 7q and 1q are associated with the GCB subtype, whereas the anomalies observed in the sub-type ABC are the gains 3/3q, 18/18q (or even amplification of *BCL2*), 19q and deletions 6q and 9p.¹⁷ The translocations involving *BCL6* are distributed in the two subtypes GCB and ABC, although the t(3;14) *IGH-BCL6* is more frequently associated with the ABC subtype. These distinct cytogenetic profiles suggest the existence of two distinct oncogenic pathways in DLBCLs. *MYC* rearrangements are also present in the two subtypes GCB and ABC.¹⁸

NGS studies of DLBCL identified somatic mutations in genes involved in epigenetic remodelling (*CREBBP/p300*, mutated in 35% of cases; *KMT2D/MLL2*, mutated in 30% of cases; *EZH2*, mutated in 22% of GCB subtype DLBCL) or in the mechanisms of immune escape (*B2M*, mutated or deleted in 30% of cases; *CD58* mutated or deleted in 20% of cases). Some mutations are specifically associated with a subtype of DLBCL, arguing for distinct oncogenic pathways: mutations of *BCL2*, *BCL6*, *MEF2B*, *EZH2* are associated with the GCB subtype, whereas mutations of *CD79a/CD79b*, *MYD88*, *TNFAIP3 (A20)*, *BLIMP1* and *CARD11* are associated with the non-GCB subtype and cause constitutive activation of the NF- κ B pathway.¹⁹

HIGH-GRADE B-CELL LYMPHOMA

The characterisation of borderline entities has been debated for decades. The WHO 2001 classification proposed the Burkitt-like variant within the Burkitt entity. The WHO 2008 classification introduced a new provisional entity named 'B-cell lymphoma, unclassifiable' (BCLU) with features intermediate between DLBCL and BL.³

It is a rare diagnosis (3% of cases of B-cell lymphoma), often described in the elderly, with a heterogeneous, aggressive clinical presentation, a high frequency of extranodal localisations and an unfavourable prognosis.^{20,21} There is no morphological or IHC criterion to formally determine the diagnosis, although most of these tumours have a very high proliferation index (Ki-67 >90%) and are more frequently listed as GCB subtype according to the Hans classification. The GEP of BCLUs also shows intermediate characteristics between BL and DLBCL. Cytogenetically, the karyotype is often complex, with a high frequency of rearrangements of *MYC* (35-90% according to the studies) associated with *BCL2* and/or *BCL6* (35-75% of cases, according to studies). Recent molecular arguments based on transcriptomic data reinforce the status of aggressive B-cell lymphoma, with 66% *ID3* gene mutations (less biallelic mutation than BL), 50% *MYC* mutations and 29% *CCND3* mutations.²² This provisional category has been eliminated and replaced by two new provisional entities of high-grade B-cell lymphoma (HGBL) in the 2016 revision of the WHO classification.^{1,2}

High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements

This new entity includes 'double-hit (DH)/triple-hit (TH)' lymphomas other than follicular lymphoma and lymphoblastic lymphomas. These lymphomas are defined by the existence of a double or triple rearrangement of oncogenes, one of which involves *MYC*: most often it is DH *MYC/BCL2*, more rarely DH *MYC/BCL6* or TH *MYC/BCL2/BCL6*.^{1,2} Most of these DH or TH have a *MYC*-non-IG rearrangement within a very complex karyotype and are usually associated with a very aggressive course with an overall survival (OS) of less than 12 months.^{23,24} DH *MYC/BCL2* is frequently classified as GCB, whereas DH *MYC/BCL6* usually shows a non-GCB subtype.¹⁸

High-grade B-cell lymphoma, not otherwise specified

This entity is dedicated to a blastoid-appearing large B-cell lymphoma lacking *MYC*, *BCL2* or *BCL6* translocations that was previously called BCLU because of the intermediate characteristics between DLBCL and BL.^{1,2}

CYTOGENETIC AND MOLECULAR MARKERS IN PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA AND HODGKIN LYMPHOMA

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

PMBL and classical Hodgkin lymphoma (cHL) have common genetic aberrations including alterations of chromosome 9p24 involving *PD-L1/PD-L2/JAK2* genes and mutations in multiple genes such as *PTPN1*, *B2M*, *TNFAIP3*.²⁵⁻²⁷ Recently, a mutation in the exportin-1 gene (*XPO1*^{E571K}), a pivotal eukaryotic nuclear export protein, has been described in about 25% of both PMBL and cHL and represents also a promising therapeutic target.²⁸

HODGKIN LYMPHOMA

Cytogenetic tools usually exhibit aneuploidy of the Hodgkin-Reed-Sternberg (HRS) cells with a frequent polyploidy. Copy-number arrays reveal recurrent gains including 2p, 9p and 12q.²⁶ The 9p24.1 region includes *JAK2* but also *CD274/PDL1* and *PDCD1LG2/PDL2*. *PD-L1/PD-L2* alterations are a defining feature of cHL and represent therapeutic targets with good clinical results in refractory cHL.²⁹ Whole-exome sequencing of purified Hodgkin-Reed-Sternberg cells has shown inactivating mutations of the *B2M* gene as being the most frequently mutation detected in HL and could be associated with better OS in HL.²⁷

CYTOGENETIC AND MOLECULAR MARKERS IN B- AND T-LYMPHOBLASTIC LYMPHOMA

B-LYMPHOBLASTIC LYMPHOMA

B-lymphoblastic lymphoma (B-LBL) is a rare neoplasm of precursor cells (lymphoblasts) of B-cell origin, grouped together with acute lymphoblastic leukaemia (ALL). Although only a limited number of cytogenetic studies of B-LBL are reported in literature, the distribution of chromosomal aberrations seems to differ from that of B-ALL. Some of the characteristic cytogenetic changes seen in B-ALL were not detected in B-LBL, such as *t(9;22)(q34;q11)/BCR-ABL*, *t(4;11)(q21;q23)/KMT2A-AFF1*, *t(12;21)(p13;q22)/ETV6/RUNX1*, *t(1;19)(q23;p13)/TCF3-PBX1* (3-5%) and hyperdiploidy. In contrast, additional chromosome 21 material, such as trisomy, tetrasomy or *add(21)(q22)*, is proportionally more frequent in B-LBL than in B-ALL.³⁰

T-LYMPHOBLASTIC LYMPHOMA

In contrast to ALL, T-lymphoblastic lymphoma (T-LBL) constitutes the large majority of LBL (~90%). Compared with ALL, there are few data on the role and the specificity

of cytogenetics or molecular analysis. Chromosomal translocations involving the different T-cell receptor loci (*TCR α / β / δ / γ*) on chromosomes 7 and 14 are common among T-LBL, but apart from a rare *t(9;17)* translocation specific to T-LBL and translocations of the 9q34 chromosomal region enriched in T-LBL, there is no specific cytogenetic profile observed in most cases.^{30,31} The *t(9;17)* translocation carries prognostic significance as it has been associated with an aggressive clinical course.³¹

The very rare association of T-LBL with peripheral blood or bone marrow eosinophilia should prompt a search for *FGFR1* gene rearrangement by FISH. Although very rare, the *NUP214-ABL1* chimeric gene amplification should also be identified in T-LBL as this aberration is easily detected by FISH and targetable with tyrosine kinase inhibitors.^{32,33} The same therapeutic approach can be employed in the very rare but well-documented cases of T-LBL carrying the *BCR-ABL1* translocation, previously described as the lymphoblastic crisis of Philadelphia chromosome-positive ALL. Among the different molecular abnormalities identified in T-LBL, *NOTCH1* and *FBXW7* gene mutations are currently the most convincing prognostic indicators for T-LBL, and a 4-gene prognostic model including *NOTCH1*, *FBXW7*, *RAS* and *PTEN* has been recently proposed by the GRAALL-LYSA group as a useful tool to identify aggressive forms of T-LBL.^{32,33} *NOTCH1/FBXW7* mutations in the absence of *RAS* mutation or *PTEN* mutation/alteration represent a molecular combination associated with a good prognosis, whereas lack of *NOTCH1/FBXW7* mutations or presence of *RAS* or *PTEN* alterations predict a very poor outcome.³⁴ This molecular prognostic model nevertheless awaits validation in larger cohorts of patients before being implemented in routine.

CYTOGENETIC AND MOLECULAR MARKERS IN MATURE T- AND NK-CELL LYMPHOMAS

As introduction to this chapter, it can be said that *IG* and *TCR* clonality tests have more utility in the diagnostic workup of T-cell lymphoma than in the B-cell counterpart, because an accurate diagnosis of T-cell lymphoma can be challenging. Although *IG/TCR* gene rearrangements are not markers for lineage (see chapter 'B- and T-cell clonality tests' in part 1 of this review), the identification of a T-cell monoclonality in the absence of B-cell monoclonality is of help for making a final diagnosis of lymphoma of T-cell origin. Nevertheless, it must be reminded that configuration of *TCR* gene may be germline in NK cell neoplasms and some cases of anaplastic lymphoma kinase (ALK)-negative anaplastic large cell lymphoma (ALCL).

TABLE 1. Main characteristics of the different categories of aggressive B-cell lymphomas according to the 2016 revised version of the World Health Organization classification.¹

Characteristic	BL	BLL 11q*	DLBCL-NOS	HGBL DH/TH	HGBL-NOS**
Proliferation (KI67)					
>90% and homogeneous	yes	yes	rare	common	common
<90% or heterogeneous	no	no	common	sometimes	sometimes
BCL2 expression					
Negative/weak	yes	yes	sometimes	sometimes	sometimes
Strong	no	no	sometimes	sometimes	sometimes
Genetic features					
Simple karyotype	yes	yes	rare	rare	rare
Complex karyotype	rare	rare	common	common	common
MYC R	yes SH IG-MYC	no	rare SH IG & non-IG-MYC	yes DH/TH*** IG & non-IG-MYC	rare SH IG & non-IG-MYC
BCL2 R without MYC R	no	no	15%	no	sometimes
BCL6 R without MYC R	no	no	30%	no	sometimes

*cases that closely resemble BL but lack *MYC* rearrangement, **cases that appear blastoid or intermediate between DLBCL and BL but which lack *MYC* and *BCL2* and/or *BCL6* rearrangement, ****MYC* and *BCL2* and/or *BCL6* rearrangement.
BL: Burkitt lymphoma, *BLL*: Burkitt-like lymphoma, *DLBCL-NOS*: diffuse large B-cell lymphoma, not otherwise specified, *HGBL DH/TH*: high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements, *HGBL-NOS*: high grade B-cell lymphoma, not otherwise specified, *SH*: simple hit, *DH/TH*: double hit/triple hit, *R*: rearrangement.

As known, T-cell lymphomas are divided into precursor T-cell (lymphoblastic) neoplasms (T-LBL) and mature post-thymic lymphomas, hence peripheral T-cell lymphomas (PTCLs) or mature T and NK neoplasms. T-LBL has been discussed previously.

This next review will be limited to the more common entities with exclusion of primary cutaneous lymphomas.

PERIPHERAL T-CELL LYMPHOMA, NOT OTHERWISE SPECIFIED

PTCL is a heterogeneous category of nodal and extranodal mature T-cell lymphoma, which is mainly defined by exclusion of the specifically defined entities of mature T-cell neo-

plasms. GEP and massive parallel sequencing (MPS) studies have brought robust diagnostic molecular signatures allowing to make a more accurate diagnosis and a better classification among the different clinical and morphological subsets of PTCL.³⁴ They have also identified molecular subgroups with specific oncogenic pathways that could serve as a diagnostic tool and/or could be considered as potential targets to novel and more efficient therapies. Nevertheless, there is still some way to go before being able to give a clear picture of all PTCL subsets.

Three distinct molecular subgroups of PTCL-NOS (not otherwise specified) have been delineated by GEP analyses. They are associated with different clinical behaviours and

TABLE 2. Relevant genetic biomarkers for the clinical management of aggressive B-cell lymphomas.

Lymphoma entities	Mandatory	Optional or recommended	Under development
BL	MYC/8q24 R ^(1,2) In adult patients: BCL2/18q21 R ^(1,2) BCL6/3q27 ^(1,2)	Degree of complexity of the genomic aberrations ^(1,3) If MYC R: → IG/MYC R ^(1,2) **	Gene expression profile ⁽⁷⁾ Mutational landscape ⁽⁵⁾ (TCF3, ID3, CCND3, TP53, CDKN2A, MYC, DDX3X, PTEN, PIK3R1, ARID1A, SMARCA4, GNA13, ROCK1)
BLL 11q	MYC/8q24 R ^(1,2) In adult patients: BCL2/18q21 R ^(1,2) BCL6/3q27 ^(1,2)	Degree of complexity of the genomic aberrations ^(1,3) 11q/gain + loss ⁽³⁾	Gene expression profile ⁽⁷⁾ Mutational landscape ⁽⁵⁾ (No published series)
DLBCL-NOS	MYC/8q24 R ^(1,2) BCL2/18q21 R ^(1,2) BCL6/3q27 ^(1,2)	Degree of complexity of the genomic aberrations ^(1,3) If MYC R: → IG/MYC R ^(1,2) → TP53/17p13 ⁽¹⁻⁴⁾ → CDKN2A/9p21 ^(1,3) If T / histiocyte rich: → 2p11, 9p11 ^(1,2) If leg-type: → + CDKN2A/B/9p21	Gene Expression profile ^{(7)**} Mutational landscape ⁽⁵⁾ (KMT2D, KMT2C, CREBBP, B2M, TNFAIP3, MYD88, PIM1, EP300, MEF2B, SOCS1, TP53, CIITA, ITPKB, GNA13, STAT6, TNFRSF14, CD79B, CD58, BCL2, CARD11, EZH2, NOTCH2, MYC, XPO1, NOTCH1, BRAF, SGK1, PRDM1, B2M, CD58)
HGBL, DH/TH HGBL-NOS	MYC/8q24 R ^(1,2) BCL2/18q21 R ^(1,2) BCL6/3q27 ^(1,2)	Degree of complexity of the genomic aberrations ^(1,3) If MYC R: → IG/MYC R ^(1,2)	Gene expression profile ⁽⁷⁾ Mutational landscape ⁽⁵⁾ (No published series)
PMBL		9p24/PD-L1, PD-L2, JAK2 alteration ^(1,2)	Mutational landscape ⁽⁵⁾ XPO1, PTPN1, B2M, TNFAIP3, etc.
HL		9p24/JAK2 alteration ^(1,2)	

⁽¹⁾classical karyotype, ⁽²⁾ fluorescent in situ hybridisation, ⁽³⁾ molecular karyotyping (based on the CGH-array or the SNP-array approach), ⁽⁴⁾PCR, ⁽⁵⁾MPS, ⁽⁶⁾MLPA, ⁽⁷⁾GEP, ^{*}identification of the partner locus of translocations and especially to discriminate between the IG/MYC versus the non-IG/MYC rearrangements (the IG loci are 14q32/IGH, 2p11/IGK, 22q11/IGL), ^{**}among the DLBCL-NOS, the distinction between the germinal centre B-cell-like type versus the activated B-cell-like/non-GC type is now required as it may affect therapy. The use of a technical surrogate such as immunohistochemistry ('Hans algorithm') is acceptable, but it has no 100% concordance with the GEP profile, ^{***}the long-distance PCR has been developed for the MYC fusion genes in the frame of clinical trials (AIEOP, COG, LMB) for the assessment of the minimal disseminated disease and the minimal residual disease in children and adolescents with BL and DLBCL, but it is not suitable in routine molecular laboratories, yet.

BL: Burkitt lymphoma, BLL: Burkitt-like lymphoma, DLBCL-NOS: diffuse large B-cell lymphoma, not otherwise specified, HGBL DH/TH: high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements, HGBL-NOS: high grade B-cell lymphoma, not otherwise specified, SH: simple hit, DH/TH: double hit/triple hit, PMBL: primary mediastinal B-cell lymphoma, HL: Hodgkin lymphoma, PCR: polymerase chain reaction, R: rearrangement.

responses to therapy. A first subgroup shows high expression of *TBX21* (49% of PTCL-NOS), a second subset shows overexpression of *GATA3* (33% of PTCL-NOS) and a third 'unclassified' group comprises the cases negative for both *GATA3*- and *TBX21*-gene signature (18% of PTCL-NOS).³⁴ Of note, *GATA3* gene overexpression can be detected by IHC. This molecular profile has also a prognostic implication, with the *GATA3* overexpression being associated with an aggressive disease, whereas the clinical behaviour of the *TBX21*-subgroup will vary according to the gene sub-signature observed (a remarkably good prognosis associated with a high plasma cell-like gene signature but a poor outcome for patients expressing a high cytotoxic cell-like signature).³⁵ GEP studies have also identified constitutive activation of the NF- κ B and STAT3 pathways that could be addressed by new targeted therapies.³⁴

Gene fusions can be observed in subsets of PTCL-NOS cases, such as *CTLA4-CD28* gene fusion or *VAV1* gene fusion with varying partners. In-frame deletion (*VAV1* Δ 778-786) can also induce activation of the *VAV1* signalling, supporting a driver oncogenic role of this pathway in the pathogenesis of at least 10-15% of PTCL cases.³⁷

ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA AND OTHER NODAL LYMPHOMAS OF T FOLLICULAR HELPER CELL ORIGIN

Angioimmunoblastic T-cell lymphoma

Angioimmunoblastic T-cell lymphoma (AITL) demonstrates a specific GEP profile that enables to distinguish AITL from other PTCL. It is dominated by a micro-environmental pattern characterised by either a B-cell signature or an immunosuppressive signature.^{34,39,40} This profile permits reclassifying a substantial number of PTCL-NOS cases (at least 18%) as AITL, some of which eventually presenting with morphological features compatible with AITL upon consensus review.^{34,39,41} Those with a B-cell signature seem to have a good prognosis, whereas those with an immunosuppressive signature show a poor clinical outcome.^{34,39}

NGS studies have identified frequent mutations of genes encoding epigenetic modifiers such as *TET2* (50-80%), *DNMT3A* (20-30%), *IDH2* (20-30%) as well as the small GTPase *RHOA* (60-70%).³⁷⁻³⁹ *RHOA*^{G17V} and *IDH2*^{R172} mutations are genetic variants that are relatively specific for AITL and may thus serve as diagnostic biomarkers. *TET2* mutations are associated with a more aggressive disease.^{39,40,42,43}

AITL harbours no specific chromosomal abnormalities. Cytogenetic investigations are thus optional in AITL and without significant aid to diagnostic workup. Molecular cytogenetic (single nucleotide polymorphism [SNP] arrays) studies have nevertheless demonstrated specific regions of

frequent copy number gains, with emphasis on amplification of 7p22 and 13q22 chromosomal regions leading to subsequent overexpression of *CARMA1* and *MYCBP2* genes, respectively, associated with poor prognosis.³⁴ Lastly, a *CTLA4-CD28* gene fusion (identical to the one described in PTCL-NOS) is observed in a subset of AITL and is a potential target for anti-CTL4 immunotherapy.³⁹

Follicular T-cell lymphoma

A recurrent t(5;9)(q33;q22) chromosomal translocation leading to *ITK-SYK* fusion is observed in 20% of follicular T-cell lymphoma (FTCL).^{2,36} It seems to be specific of this entity. The detection of *RHOA*, *TET2* and *DNMT3A* mutations demonstrates overlapping genetic characteristics with AITL.³⁹

Nodal peripheral T-cell lymphoma with T follicular helper phenotype

GEP and MPS studies have also made a contribution to reclassifying a significant portion of PTCL previously considered as NOS that appears to share the same T-follicular helper (T_{FH}) phenotype and mutational landscape with AITL. This subset of nodal PTCL with T_{FH} phenotype (NPTCL-T_{FH}) is now included in the WHO 2017 classification as a provisional entity.² The common *TET2/DNMT3A/RHOA* mutational profile that is observed in AITL and NPTCL-T_{FH} can be used to distinguish these two entities from the remaining PTCL-NOS group.³⁸ *IDH2* mutations seem to be restricted to AITL.³⁹

ANAPLASTIC LARGE CELL LYMPHOMA

In this paragraph, the description will be limited to the systemic ALK-positive and ALK-negative nodal ALCL.

ALK-positive anaplastic large cell lymphoma

By definition, this entity exhibits a characteristic *ALK* oncogene rearrangement leading to its subsequent overexpression and constitutive/aberrant tyrosine kinase activity.⁴⁴ It is more common in children and young adults and associated with a good prognosis unlike ALK-negative ALCL and most other PTCL subtypes. The *ALK* rearrangement is most often due to a t(2;5)(p23;q35)/*NPM-ALK*+, accounting for around 80% of ALK-positive cases. In the remaining 20% of cases, *ALK* locus translocates with various partner genes such as *TPM3* on 1q25, *ATIC* on 2q35 and *TFGX* on 3q11.⁴⁴ The clinical relevance of identifying the different *ALK* fusion partners involved in the translocation remains a matter of debate. Opinion leaders believe that some of the gene partners result in a less favourable prognosis, and, therefore, the patients could benefit from a more intensive treatment.

TABLE 3. Relevant genetic biomarkers for the clinical management of mature T- and NK-cell lymphomas.

Lymphoma entities	Mandatory	Recommended/optional	Under development
PTCL-NOS		Gene expression profile ^{(6)**} (TBX21, GATA3, PDGFRA, etc.) <i>CTLA4-CD28</i> , <i>VAV1</i> ^(2,4)	Mutational landscape ⁽⁵⁾ (<i>FYN</i> , <i>VAV1</i> , etc.)
AITL		7p22 and 13q22 amplification ⁽³⁾ (<i>CARMA1</i> and <i>MYCBP2</i>) <i>CTLA4-CD28</i> ^(2,4)	Mutational landscape ⁽⁵⁾ (<i>TET2</i> , <i>DNMT3A</i> , <i>RHOA</i> , <i>IDH2</i>)
FTCL		t(5;9)/ <i>SYT-ITK</i> ^(1,2)	Mutational landscape ⁽⁵⁾ (<i>TET2</i> , <i>DNMT3A</i> , <i>RHOA</i>)
NPTCL-TFH		Gene expression profile ^{(6)**}	Mutational landscape ⁽⁵⁾ (<i>TET2</i> , <i>DNMT3A</i> , <i>RHOA</i>)
ALCL		<i>ALK</i> R ^{(1,2)*} <i>DUSP22</i> R ^(1,2) <i>TP63</i> ^(1,2) '3 genes set' in ALK- ALCL ⁽⁵⁾ (<i>TNFRSF8</i> , <i>BATF3</i> and <i>TMOD1</i>) ^{**}	Mutational landscape ^(4,5) (<i>DDX3X</i> , <i>JAK3</i> , <i>TP53</i> , <i>STAT3</i> , <i>STAT5B</i> , etc.) del(6q21) and/or del(17p13) ⁽³⁾ (<i>PRDM1</i> and <i>TP53</i>)
NKTCL		<i>CTLA4-CD28</i> ^(2,4) del(6q21) (<i>PRDM1</i>) ⁽³⁾	Mutational landscape ⁽⁵⁾ (<i>DDX3X</i> , <i>JAK3</i> , <i>TP53</i> , <i>STAT3/5B</i> , etc.)
ATLL		del(9p) (<i>CDKN2A</i>) ^(1,2) <i>TP53</i> ⁽⁵⁾	Mutational landscape ⁽⁵⁾ (<i>PLCG1</i> , <i>PRKCB</i> , <i>CARD11</i> , <i>FYN</i> , <i>CCR4</i> , <i>CCR7</i>)
HSTCL		i(7)(q10) ^(1,2)	Mutational landscape ⁽⁵⁾ (<i>SETD2</i> , <i>INO80</i> , <i>ARID1B</i> , <i>STAT5B</i> , <i>STAT3</i> , <i>PIK3CD</i> , etc.)
ITL*		1q24-44, 5q, 8q24, 9q33-34, gains ^(1,2,3)	Mutational landscape ⁽⁵⁾ (<i>JAK/STAT</i> , <i>RAS</i> pathways, etc.)
T-LBL	<i>NUP214-ABL</i> ^(2,3) <i>BCR-ABL1</i> ^(1,2)	t(9;17) ^(1,2) t(9q34) ^(1,2)	Mutational landscape ^(3,4,5) (<i>NOTCH1</i> , <i>FBXW7</i> , <i>RAS</i> and <i>PTEN</i>)

⁽¹⁾classical karyotype, ⁽²⁾fluorescent in situ hybridisation, ⁽³⁾molecular karyotyping (based on the CGH-array or the SNP-array approach), ⁽⁴⁾conventional (RT)PCR, ⁽⁵⁾MPS, ⁽⁶⁾GEP, *the nuclear and/or cytoplasmic ALK protein overexpression subsequent to the *ALK* gene rearrangement is a hallmark of this lymphoma subset, and its detection by immunohistochemistry in a lymphoid tumour represents a highly sensitive and specific test, correlating in nearly 100% of cases with the presence of *ALK* rearrangement, **the clinical interest of this method is well demonstrated, but it is nevertheless not suitable for routine use and has currently not been replaced by other techniques easy to apply (such as immunohistochemistry).

PTCL-NOS: peripheral T-cell lymphoma, not otherwise specified, *AITL*: Angioimmunoblastic T-cell lymphoma, *FTCL*: follicular T-cell lymphoma, *NPTCL-TFH*: nodal peripheral T-cell lymphoma with T follicular helper phenotype, *ALCL*: anaplastic large cell lymphoma, *ALK*: anaplastic lymphoma kinase, *NKTCL*: extranodal NK/T cell lymphoma, nasal type, *ATLL*: adult T-cell leukaemia/lymphoma, *HSTCL*: hepatosplenic T-cell lymphoma, *ITL*: intestinal T-cell lymphoma, *T-LBL*: T-lymphoblastic lymphoma, *PCR*: polymerase chain reaction, *R*: rearrangement.

ALK-aberrant tyrosine kinase activity enhances cell proliferation and survival through activation of several signalling cascades including PI3K/AKT/mTOR, JAK/STAT3, RAS/ERK that represent good candidates for new targeted therapies.^{45,46}

ALK-negative anaplastic large cell lymphoma

GEP studies have shown that ALK-negative ALCL has a signature similar to that of ALK-positive ALCL but different from other PTCL. A set of six genes, comprising of *TNFRSF8*(*CD30L*), *BATF3*, *TMOD1*, *TMEM158*, *MSC* and *POPDC3* were identified to be highly informative in discerning ALK-negative ALCL patients.⁴⁷ Based on this set, a model limited to three genes (*TNFRSF8*, *BATF3*, and *TMOD1*) has been designed and validated by RT-qPCR to clearly differentiate ALK-negative ALCL from PTCL-NOS, including CD30⁺ PTCL-NOS. This three-gene model was successfully applied to fresh and formalin-fixed paraffin-embedded samples with an overall accuracy near 97%.⁴⁸ It is currently not in routine practice and a more practical methodology such as IHC is still awaited as surrogate for RT-qPCR. Lastly, a new subclass of ALK-negative ALCL (24% of cases) was recently defined, based on aberrant co-expression of *ERBB4* and *COL29A1* genes.⁴⁸

Recurrent chromosomal rearrangements involving the *DUSP22-IRF4* locus on chromosome 6p25.3 or the TP63 locus (the TP53 homologue) on chromosome 3q28 are observed in 30% and 8% of ALK-negative ALCLs, respectively.^{49,50} *DUSP22* and *TP63* rearrangements can serve as diagnostic tools as they are seen almost exclusively in ALK-negative ALCL. They have also significant prognostic associations, with *DUSP22* disruption showing a favourable outcome (a 90% five-year overall survival [OS]), similar to ALK-positive cases, while *TP63* rearrangements are very unfavourable (a 17% five-year OS) with nearly uniform failure to standard therapies (CHOP regimen, without consolidative autologous stem cell transplantation [ASCT]).^{51,52} Triple negative ALCL (hence, ALK-, *DUSP22*- and *TP63*-negative cases) have an intermediate five-year OS rate of 42%. These preliminary studies seem also to indicate that the *DUSP22*-rearranged ALCL subgroup that responds well to CHOP therapy might not benefit from consolidative ASCT in first remission.⁵² This observation nevertheless awaits validation in larger patient cohorts. For a sake of completeness, one also must be aware that *DUSP22* rearrangement can also be seen in primary cutaneous ALCL and lymphomatoid papulosis. The prognostic impact of the abnormality in the context of both last diseases is not known.

Losses of 6q21 and/or 17p13 chromosomal regions with subsequent deletion of the *PRDM1* and *TP53* loci are ob-

served in 29% and 52% of the ALK-negative cases, respectively, and both deletions co-occur in one-quarter of the cases.⁵³ All cases had a poorer outcome but these clinical observations require further validation due to the relatively limited series of evaluable cases and the heterogeneous type of given treatment.⁵³

Lastly, the recurrent activating mutations of *JAK1* and/or *STAT3* as well as the existence of chimeric genes combining a transcription factor (such as *NF-κB2* or *NCOR2*) with a tyrosine kinase (*ROS1* or *TYK2*) are observed in about 38% of ALK-negative cases and lead to constitutive activation of the JAK/STAT3 pathway. Those different genetic alterations thus represent sensitive therapeutic targets to JAK/STAT inhibitors.⁵⁴

EXTRANODAL NK/T CELL LYMPHOMA, NASAL TYPE

Different somatic mutations have been observed in NK/T cell lymphoma, nasal type (NKTCL), with the most common being mutations of the ATP-dependent RNA helicase gene *DDX3X* (20% of cases), *JAK3* (35% of cases) and *TP53* (18-24% of cases).^{34,39} Mutations of *STAT5B* and *STAT3* genes have also been identified in NKTCL, further emphasising the role of the JAK/STAT3 pathway in PTCL. Among structural aberrations, the *CTLA4-CD28* fusion gene may be identified in NKTCLs as well as a deletion at the 6q21 chromosomal region with subsequent loss of the *PRDM1* gene.³⁹

ADULT T-CELL LEUKAEMIA/LYMPHOMA

Adult T-cell leukaemia/lymphoma (ATLL) shows a very complex cytogenetic profile involving potentially every chromosomal pair but without specific changes that could be helpful in making the diagnosis.⁵⁵

GEP analysis has showed overexpression of genes linked to the cell cycle (*CDC2*, *cyclin B*), calcium metabolism (*RANKL*, *PTHLH*), tyrosine kinase signalling pathways (*SYK*, *LYN*) and anti-apoptotic factors such as *BIRC5/survivin* gene. The anti-apoptotic function of *BIRC5* could explain the resistance of ATLL cells to chemotherapy and makes this gene a rational clinical target in the treatment of ATLL.⁵⁶ Lastly, some molecular abnormalities such as *CDKN2* gene deletion and *TP53* mutation are observed in about half of the cases and are associated with a more aggressive disease.⁵⁵

HEPATOSPLENIC T-CELL LYMPHOMA

The $\gamma\delta$ and $\alpha\beta$ hepatosplenic T-cell lymphoma (HSTCL) show a very similar GEP and genomic profile, indicating that both variants could be grouped into a single lymphomatous entity.⁵⁷ These molecular patterns are characterised in particular by an overexpression of genes encoding KIR molecules

KEY MESSAGES FOR CLINICAL PRACTICE

- 1** In case of an aggressive B-cell lymphoma in adult patients (Burkitt lymphoma [BL], diffuse large B-cell lymphoma [DLBCL], high-grade B-cell lymphoma [HGBCL]), the rearrangements of *MYC*, *BCL2* and *BCL6* oncogenes should be sought by fluorescent in situ hybridisation (FISH), for diagnosis and prognosis purposes.
- 2** In case of childhood mature B-cell lymphoma (mainly BL and DLBCL), it is only necessary to search for a *MYC* rearrangement (by FISH).
- 3** In case of aggressive lymphoma with histological features of BL but without detection of a *MYC* rearrangement (with the use of appropriate FISH probes), it is recommended to look for a 11q gain/loss alteration by molecular karyotyping to identify the new provisional entity of Burkitt-like lymphoma with 11q alteration.
- 4** In the rare cases of B-lymphoblastic lymphoma, the same genetic tests as for B-cell acute lymphoblastic leukaemia [t(9;22)/BCR-ABL, t(4;11)/KMT2A-AFF1, t(12;21)/ETV6/RUNX1, t(1;19)/TCF3-PBX1, hyperdiploidy, hypodiploidy] have to be systematically carried out for prognostic assessment, although not detected, yet.
- 5** In T-lymphoblastic lymphoma (T-LBL), rare cases exhibit a specific t(9;17), associated with a poor prognosis. Although very rare in T-LBL, a search for the *NUP214-ABL1* chimeric gene amplification as well as for the *BCR-ABL1* chimeric gene must be made as both aberrations are targetable with tyrosine kinase inhibitors.
- 6** The identification of a T-cell monoclonality in absence of B-cell monoclonality is of help for making a final diagnosis of lymphoma of T-cell origin. Nevertheless, one must be aware that TCR genes may not be rearranged (no T-cell clonality) in NK cell neoplasms and some cases of anaplastic lymphoma kinase (*ALK*)-negative anaplastic large cell lymphoma (ALCL).
- 7** Angioimmunoblastic T-cell lymphoma (AITL) shares a common *TET2*/*DNMT3A*/*RHOA* mutational profile with the nodal peripheral T-cell lymphoma with T follicular helper phenotype. This profile allows distinguishing these two subgroups from peripheral T-cell lymphoma, not otherwise specified. *IDH2*^{R172} mutation is relatively specific for AITL and may thus serve as a diagnostic biomarker. *TET2* mutations are associated with a more aggressive disease. In follicular T-cell lymphoma, a recurrent t(5;9)(q33;q22)/*SYK*-*ITK*+ chromosomal translocation is found in around 20% of cases and represents a good diagnostic biomarker of this new 2017 WHO entity.
- 8** *ALK*-positive ALCL is a lymphoma subgroup with a good prognosis. It is mostly observed in children and young adults. In *ALK*-negative ALCL, a *DUSP22* gene rearrangement is associated with a good prognosis, similar to *ALK*-positive ALCL. In contrast, the *ALK*-negative cases presenting with a *TP63* gene rearrangement (8%) define a cytogenetic subgroup of poor prognosis, with refractoriness to standard chemotherapy (CHOP).
- 9** In hepatosplenic T-cell lymphoma (HSTCL), there are good molecular arguments to consider that $\gamma\delta$ and $\alpha\beta$ HSTCL are part of the same lymphomatous entity. An isochromosome 7q [i(7)(q10)] is a recurrent cytogenetic abnormality in HSTCL and allows, in most cases, to discriminate HSTCL from other T-cell non-Hodgkin lymphomas.
- 10** In intestinal T-cell lymphoma, genomic imbalances may help differentiating enteropathy-associated T-cell lymphoma (1q and 5q gains) from monomorphic epitheliotropic intestinal T-cell lymphoma (8q24 gain).

(such as *KIR3DS1*). Moreover, these patterns appear to be unique to ($\gamma\delta$ and $\alpha\beta$) HSTCL, allowing this T-cell lymphoma subtype to be distinguished from other T-cell non-Hodgkin lymphoma (NHL).⁵⁷

Whole-exome sequencing studies have recently unravelled the genetic landscape of HSTCL which is characterised by mutations involving chromatin-modifying genes including *SETD2*, *INO80*, and *ARID1B* as the most commonly mutated genes (62% of cases).⁵⁸ Mutations of genes that are potential treatment targets, including *STAT5B* (31%), *STAT3* (9%) and *PIK3CD* (9%) genes, were also recurrently observed.⁵⁹ Within this mutational profile, *SETD2* gene mutation appears to be specific to $\gamma\delta$ HSTCL.

Fifty to eighty percent of the $\gamma\delta$ HSTCL demonstrates the presence of an isochromosome 7q [i(7)(q10)] that can also be encountered in $\alpha\beta$ HSTCL, although to a much lesser extent (around 15%).^{58,59} The i(7q) is thus a relatively good cytogenetic marker for HSTCL among other T-cell NHL (although it has been observed in rare cases of extranodal NK/TCL and ALCL).

INTESTINAL T-CELL LYMPHOMA

Unlike other mature T-cell lymphomas, both intestinal T-cell lymphoma (ITL) subtypes, enteropathy-associated T-cell lymphoma (EATL; previously designed as EATCL type I) and monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL; previously named EATCL type II) harbour either 9q33-q34 chromosomal region gains (including several known oncogenes, such as *NOTCH1*, *ABL1*, *VAV2*) or 16q23.1 chromosomal region deletions in nearly 80% of cases. The continuum between the refractory coeliac disease and the EATL is illustrated by the common 1q24-q44 trisomy observed in 90% and 75% of cases, respectively. Microarray studies also showed that 1q and 5q gains are relatively characteristics of EATL while 8q24 gains are rather observed in MEITL.⁶¹ Recent studies have revealed the frequent mutations of the JAK/STAT pathway (50% of EATL and 80% of MEITL) and the RAS signalling (20% and 32%, respectively) in the ITL.⁶² The predominant JAK/STAT mutations seem to involve *JAK1* and *STAT3* in EATL and *JAK3* and *STAT5B* in MEITL.⁶²

CONCLUSION

The importance of genetic markers in the diagnosis of aggressive B and to a lesser extent of T/NK-cell lymphomas is now recognised as a component of the current sub-classifications in the recent 2016 revision of the WHO classification of lymphoid neoplasms. Those markers are complementary to the morphological workup and represent valuable tools for the diagnostic and/or prognostic assessment in lymphomas as well as for therapeutic strategies.

This field is rapidly evolving and the deeper characterisation of the different mutational landscapes will probably expand the genetic workup of aggressive lymphomas.

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