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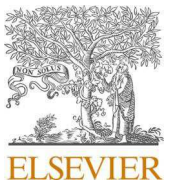

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Cytogenetics in the management of mature B-cell non-Hodgkin lymphomas: Guidelines from the Groupe Francophone de Cytogénétique Hematologique (GFCH)

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ABSTRACT

Non-Hodgkin lymphomas (NHL) consist of a wide range of clinically, phenotypically and genetically distinct neoplasms. The accurate diagnosis of mature B-cell non-Hodgkin lymphoma relies on a multidisciplinary approach that integrates morphological, phenotypical and genetic characteristics together with clinical features. Cytogenetic analyses remain an essential part of the diagnostic workup for mature B-cell lymphomas. Karyotyping is particularly useful to identify hallmark translocations, typical cytogenetic signatures as well as complex karyotypes, all bringing valuable diagnostic and/or prognostic information. Besides the well-known recurrent chromosomal abnormalities such as, for example, t(14;18)(q32;q21)/IGH::*BCL2* in follicular lymphoma, recent evidences support a prognostic significance of complex karyotype in mantle cell lymphoma and Waldenström macroglobulinemia. Fluorescence In Situ Hybridization is also a key analysis playing a central role in disease identification, especially in genetically-defined entities, but also in predicting transformation risk or prognostication. This can be exemplified by the pivotal role of *MYC, BCL2* and/or *BCL6* rearrangements in the diagnostic of aggressive or large B-cell lymphomas.
This work relies on the World Health Organization and the International Consensus Classification of hematolymphoid tumors together with the recent cytogenetic advances. Here, we review the various chromosomal abnormalities that delineate well-established mature B-cell non-Hodgkin lymphoma entities as well as newly recognized genetic subtypes and provide cytogenetic guidelines for the diagnostic management of mature B-cell lymphomas.

1. Introduction

Mature B-cell Non-Hodgkin lymphomas (NHL) represent a widely heterogeneous group of diseases both clinically and biologically. In current practice, the diagnosis of NHL can be accurately established by a multidisciplinary approach including cytomorphological, immunophenotypic, cytogenetic and molecular characteristics.

Cytogenetics have made a major contribution to refine World Health Organization (WHO) classification of NHL and improved mature B-cell lymphomas sub-classification [1,2]. In routine practice, karyotype and Fluorescence In Situ Hybridization (FISH) allow to identify both driver oncogenic events with a diagnostic value and secondary chromosomal abnormalities (CAs) that have a prognostic impact in several mature B-cell NHL.

Here, we are updating our previous recommendations for cytogenetic analysis of mature B-cell NHL [3] according to the current WHO classification of hematolymphoid tumors (WHO-HAEM5) and the International Consensus Classification (ICC) [1,2]. We describe the well-established and recently identified CAs and specify both their diagnostic relevance and their clinical impact as potential markers for prognostic stratification or risk of transformation. A short focus on key somatic mutations complement each of the described entities. Cytogenetic testing strategies are also proposed taking into account the variability of nature of the samples and the available technologies. Lastly, we briefly summarized the technical aspects of cytogenetics in the management of samples referred as lymphomas.

2. Cytogenetics and main molecular alterations in mature B-cell non-Hodgkin lymphomas and B-cell lymphoproliferative disorders

This section excludes the description of small lymphocytic lymphoma and plasmacytoma that are addressed in the same issue in papers dedicated to chronic lymphocytic leukemia and plasma cell disorders, respectively (see joint articles). Table 1 details frequency, characteristics and potential clinical relevance of primary and secondary CAs in mature B-cell lymphomas.

3. Follicular lymphoma

Follicular lymphoma (FL) is the second most common adult B-cell lymphoma in western countries. In the WHO-HAEM5, FL grade 1/2/3A are grouped together as classical FL (cFL) while FL grade 3B is now referred as follicular large B-cell lymphoma (FLBCL). A third group consists of FL with uncommon features [1].

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Table 1
Characteristics of recurrent cytogenetic abnormalities in mature B-cell lymphomas.

Pathology	Abnormalities	Frequency	Target genes	Driver derivative chromosome [a]	Commercial FISH probe(s)	Main associated features	References
Follicular lymphoma (FL)	**t(14;18)(q32;q21)**	85%	IGH::*BCL2*	der(14) [b]	IGH/BCL2, BCL2	Isolated in only 4% of FL	[4,9]
	t(2;18)(p11;q21)	2%	IGK::*BCL2*	der(18)	IGK, BCL2		
	t(18;22)(q21;q11)		IGL::*BCL2*	der(18)	IGL, BCL2		
	t(3;14)(q27;q32) or t(v;3)(v;q27)	5%	IGH::*BCL6* *v::BCL6*	der(3)	IGH, BCL6	More frequent (40%) in FL grade 3B May coexist with a *BCL2* rearrangement (10%)	[12,13]
	del(1p36)	25%	*TNFRSF14*			More prevalent in diffuse FL Frequently co-deleted with 16p13 band in diffuse FL	[14,15]
	+18/+18q	25%			BCL2	Mostly as an extra der(18)t(14;18)	[4,9]
	+X, +1q, +2p, +7, +8, +12q, +18q, del(1p), del(6q), del(10q)	10-20% each	Unknown			Combined into multiple sub-clones	
	t(8;14)(q24;q32) or t(8;v)(q24;v)	2%	IGH::*MYC* *v::MYC*	Variable	IGH/MYC, MYC, IGH	Unfavorable prognosis Up to 30% in transformed FL	[7]
Mantle cell lymphoma (MCL)	**t(11;14)(q13;q32)**	95%	IGH::*CCND1*	der(14)	IGH/CCND1, CCND1	Mostly isolated in non-nodal MCL	[21]
	t(2;11)(p11;q13)	<2%	IGK::*CCND1*	Not investigated	IGK, CCND1		[17]
	t(11;22)(q13;q11)		IGL::*CCND1*		IGL, CCND1		
	t(2;12)(p11;p13)	3%	IGK::*CCND2*	Not investigated	IGH, CCND2, IGK, IGL	t(12;14)(p13;q32) cryptic by CBA IGK::*CCND2* mostly frequent Cryptic variants (IGK, IGL) (5%)	[29,30]
	t(12;14)(p13;q32)		IGH::*CCND2*				
	t(12;22)(p13;q11)		IGL::*CCND2*				
	t(6;14)(p21;q32)	<1%	IGH::*CCND3*	Not investigated	IGH/CCND3	Rare cryptic variants (IGK, IGL)	[30]
	t(2;6)(p11;p21)		IGK::*CCND3*		IGK, IGL		
	t(6;22)(p21;q11)		IGL::*CCND3*				
	del(1p)	20-30%	Unknown		CDKN2C (1p32)	Large 1p deletion closely associated to a MCL diagnosis	[21]
	del(6q)	20-30%	Unknown		PRDM1/ TNFAIP3 (6q21/6q23)	6q deletion or i(6)(p10)	
	+3/+3q	25%	Unknown		BCL6 (3q27)		
	del(13q)	25-40%	Unknown		D13S319 (13q14)	Mostly monosomy 13	
	del(11q)	20%	*ATM*		ATM (11q22)	Sometimes on derived der (14)t(11;14)	
	del(17p)	15-20%	*TP53*		TP53 (17p13)	Significantly associated with CK	[21,22]
	+8q	5-20%	*MYC*		MYC	No clear prognostic significance	[27]
	t(8;14)(q24;q32) or t(8;v)(q24;v)	<5%	*MYC*	Variable	IGH/MYC, MYC	Unfavorable prognosis (OS) Up to 50% in blastoid and pleomorphic variants	
	del(9p21)	10-20%	*CDKN2A*		CDKN2A (9p21)	Unfavorable prognosis (OS) if associated with del(17p)/ *TP53* or *TP53* mutation	[22,25,26]
	CK >= 4 CAs including t(11;14)	59%				Up to 80% in conventional MCL Unfavorable Prognosis (OS)	[21–23]
	Chromothripsis	15-60%				60% in conventional MCL	[28]
Splenic marginal zone lymphoma (SMZL)	del(7q)	34-39%	Unknown		7q32	Usually encompassing the 7q32 band	[36,37]
	+3/+3q	25-32%	Unknown		BCL6 (3q27)		
	del(6q)	12-16%	Unknown		PRDM1/ TNFAIP3 (6q21/6q23)		
	14q32 translocation	12%	IGH		IGH,		[36,38]
	t(9;14)(p13;q32)	1.5%	IGH::*PAX5*	der(14)	PAX5,		
	t(14;19)(q32;q13) or	1.5%	IGH::*BCL3*	der(19)	BCL3,		
	t(19;v)(q13;v)	<1%	IGK::*CDK6*	der(7)	IGK, IGL,		
	t(2;7)(p11;q21)				CDK6		
	CK (≥3CAs)	50-60%				Unclear prognostic significance	
	+18/+18q	10%	Unknown		cen18		

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Table 1 (*continued*)

Pathology	Abnormalities	Frequency	Target genes	Driver derivative chromosome [a]	Commercial FISH probe(s)	Main associated features	References
	+12	8%	Unknown		cen12		
Nodal marginal zone lymphoma (NMZL)	+3/+3q	37%	Unknown		BCL6 (3q27)		[35,40,41]
	+18/+18q	28%	Unknown		cen18		
	del(6q)	19%	Unknown		PRDM1/ TNFAIP3 (6q21/6q23)		
	+1q, +6p, +12q, del (1p)	10-15%	Unknown				
Extranodal marginal zone lymphoma (EMZL)	+3/+3q	10-75%	Unknown		BCL6 (3q27)		[33,35]
	+18/+18q	4-25%	Unknown		cen18		
	t(11;18)(q22;q21)	Depending on anatomic site	*BIRC3::MALT1*	der(11)	BIRC3/MALT1, MALT1	Pulmonary (30-50%), intestinal (10-60%) and gastric (5-25%) forms For gastric forms: predictive of lack of response after Helicobacter Pylori eradication May also be observed in PCMZL	[32,33]
	t(1;14)(p22;q32)	Depending on anatomic site	IGH*::BCL10*	der(14)	IGH	Pulmonary (9%) or intestinal (4%) forms	[33,34]
	t(14;18)(q32;q21)	Depending on anatomic site	IGH*::MALT1*	der(14)	IGH, MALT1	Ocular adnexa/orbit lesions (~25%) and salivary glands (16%) Not to be confused with t (14;18) IGH::*BCL2* May also be observed in PCMZL	
	t(3;14)(p14.1;q32)	Depending on anatomic site	IGH*::FOXP1*	der(14)	IGH	Thyroid (50%) and ocular adnexa/orbit lesions (10~20%) May also be observed in PCMZL	
B-cell prolymphocytic leukemia (B-PLL)	t(8;14)(q24;q32) t(2;8)(p11;q24) t(8;22)(q24;q11) t(8;v)(q24;v)	62%	IGH::*MYC* IGK::*MYC* IGL::*MYC* *v::MYC*	Variable	IGH/MYC, MYC, IGK, IGL	Unfavorable Prognosis (OS)	[50,53]
	+8q	15%	*MYC*		MYC (8q24)	Unfavorable prognosis (OS)	[50]
	del(17p)	38%	*TP53*		TP53 (17p13)	Unfavorable prognosis (OS) if associated with a *MYC* aberration	
	+3, +12, +18, del (8p), del(13q)	20-30% each				CK (≥ 3 CAs) in 75% of cases	[50,52]
Waldenström macroglobulinemia (WM)	del(6q)	20-40%	*PRDM1, TNFAIP3*		6q21/6q23	Unfavorable prognosis (OS, PFS) Frequently associated with 6p gain	[54,58,61]
	del(13q)	10-15%	*MIR15A, MIR16-1*		D13S319 (13q14)		[54,58]
	+18/+18q	10-15%	Unknown		BCL2 (18q21)		
	+4/+4q	8%	Unknown		cen4 (or another locus on 4q)	Unfavorable prognosis (OS, PFS)	[54,57]
	del(17p)	8%	*TP53*		TP53 (17p13)	Unfavorable prognosis (OS, PFS)	[58,60]
	+12	8%	Unknown		cen12		[54,58]
	+3/+3q	6%	Unknown		BCL6 (3q27)		
	del(11q)	5%	*ATM*		ATM (11q22)		
	CK (≥3CAs), HCK (≥5CAs)	16-30%, 5%				HCK : unfavorable prognosis (OS, PFS)	[54]
Burkitt lymphoma (BL)	**t(8;14)(q24;q32)**	85%	IGH::*MYC*	Variable	IGH/MYC, MYC, IGL, IGK	Primary genetic event	[67]
	t(8;22)(q24;q11)	10%	IGL::*MYC*				
	t(2;8)(p11;q24)	5%	IGK::*MYC*				
	+1q	30%	Unknown			Duplication 1q, unbalanced or jumping translocation	
	+7, del(6q), +12, der (13), del(17p), +21	5% each	Unknown			Simple karyotype (maximum of 3 ACAs in addition to IG::*MYC*)	
Diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS)	t(3;14)(q27;q32)	10%	IGH::*BCL6*	der(3)	BCL6, IGH, IGL	Equally distributed between GCB and non-GCB subtype t (3;14)(q27;q32) associated to the non-GCB subtype	[5,76]
	t(3;22)(q27;q11)	2%	IGL::*BCL6*				
	t(2;3)(p11;q27)	rare	IGK::*BCL6*				
	t(3;v)(q27;v)	18%	*V::BCL6*				

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Table 1 (*continued*)

Pathology	Abnormalities	Frequency	Target genes	Driver derivative chromosome [a]	Commercial FISH probe(s)	Main associated features	References
	t(14;18)(q32;q21) t(2;18)(p11;q21) t(18;22)(q21;q11)	13% 2% rare	IGH::*BCL2* IGK::*BCL2* IGL::*BCL2*	der(14) [b] der(18) der(18)	IGH/BCL2, BCL2	Always in GCB subtype May coexist with a *BCL6* rearrangement in 5% of DLBCL, NOS	[72,74,75,79]
	t(8;14)(q24;q32) t(8;22)(q24;q11) t(2;8)(p11;q24) t(8;v)(q24;v)	8%	IGH::*MYC* IGL::*MYC* IGK::*MYC* non-IG::*MYC*	Variable	IGH/MYC, MYC	Secondary genetic event Not associated to *BCL2* or *BCL6* rearrangement Controversial prognostic impact	[72,74,75,79]
	+2p, +7q, +12q	15% each				Significantly associated with GCB-subtype	[71,72]
	+3/3q del(6q) del(9)(p21) +18/18q +19q	10 to 20% each	Unknown *TNFAIP3* *CDKN2A* *BCL2* *SPIB*		BCL6 (3q27) TNFAIP3 (6q23) CDKN2A (9p21) BCL2 (18q21)	Strongly correlated to non-GCB subtype *BCL2* gain correlated to aberrant expression of BCL2 protein	
Diffuse large B-cell lymphoma/ High-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements (DLBCL/ HGBL-MYC/BCL2)	t(14;18)(q32;q21) t(2;18)(p11;q21) t(18;22)(q21;q11)	100%	*BCL2*	der(14) [b] der(18) der(18)	BCL2	Always IG::*BCL2*	[72,85]
	IG::*MYC* rearrangement: t(8;14)(q24;q32) t(8;22)(q24;q11) t(2;8)(p11;q24) Non-IG::*MYC* rearrangement: t(8;v)(q24;v)	60% 40%	*MYC*	Variable	IGH/MYC, MYC, IGK, IGL	Unclear prognostic significance of *MYC* partner (IG vs *non*-IG)	[74,75,78,82]
	t(3;14)(q27;q32) t(3;22)(q27;q11) t(2;3)(p11;q27) t(3;v)(q27;v)	30%	*BCL6*	der(3)	BCL6	Should be associated with *BCL2* and *MYC* rearrangements Formerly « « triple-hit » HGBL	[5,74]
	CK	85%				The most frequent ACAs being +X, del(6q), +7, +8, +12/+12q	[82,85]
HG/DLBCL, NOS with *MYC* and *BCL6* rearrangements (HG/ DLBCL, NOS-MYC/BCL6)	t(3;14)(q27;q32) t(3;22)(q27;q11) t(2;3)(p11;q27) t(3;v)(q27;v	100%	*BCL6*	der(3)	BCL6	Equally distributed between GCB and non-GCB subtype	[5,84]
	t(8;v)(q24;v) t(3;8)(q27;q24)	100% 30%	*MYC* *BCL6::MYC*	Variable der(8)	IGH/MYC, MYC, BCL6		[86]
	CK	80%					[90]
High-grade/Large B-cell lymphoma with 11q aberration (HG/LBCL-11q)	**11q gain/loss :** **gain 11q23.3** **loss 11q24.3-q25**	100%	Unknown		Specific 11q23 /11q24 probe or CMA	Typically large 11q13-11q23 duplication-inversion with 11q24-q25 deletion	[91,93]
	CK	60%				The most frequent ACA being del(6q) and +12	
Large B-cell lymphoma with IRF4 rearrangement (LBCL-IRF4)	**t(6;14)(p25;q32)** **t(2;6)(p11;p25)** **t(6;22)(p25;q11)**	100%	IGH::*IRF4* IGK::*IRF4* IGL::*IRF4*	Not investigated	IRF4 (6p25)	t(6;14)(p25;q32) cryptic by CBA	[99,100]
	del(6q) +7 +9p	40% 35% 40%	unknown unknown unknown		6q21/6q23 cen7 JAK2, CD274/ PDCD1LG2 (9p24)	More frequent in adults In adults only	
	+11q del(17p) +18q	30% 25-70% 30%	unknown *TP53* unknown		ATM (11q22) TP53 (17p13) BCL2 (18q21)	Mostly in children More frequent in adults In adults only	
Primary mediastinal large B-cell lymphoma (PMBL)	+9p24	75%	*JAK2* *CD274 (PDL1)::v* *PDCD1LG2 (PDL2)::v*		JAK2, CD274/ PDCD1LG2 Or CMAs	Mostly isochromosome i(9)(p10)	[102,103]
	t(9;v)(p24;v)	20%	*CD274 (PDL1)::v* *PDCD1LG2 (PDL2)::v*	der(9)	CD274/ PDCD1LG2	Non-specific marker of PMBL	[104]
	+2p16	45%	*REL*			Mostly associated with 9p gain	[102,103]
	t(16;v)(p13;v)	11-38%	*v::CIITA* (16p13)	der(v)		Associated with a deletion or mutation of the second	[106,107]

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Table 1 (*continued*)

Pathology	Abnormalities	Frequency	Target genes	Driver derivative chromosome [a]	Commercial FISH probe(s)	Main associated features	References
						CIITA allele Non-specific marker of PMBL	

Abbreviations: CBA, Chromosome Banding Analysis; CK complex karyotype; HCK, highly complex karyotype; OS, overall survival; PFS, progression-free survival; CA, chromosomal abnormality; PCMZL, primary cutaneous marginal zone lymphoma; GCB, germinal centre B-cell; CMA, Chromosomal microarray. Primary chromosomal abnormality in bold.

[a] Driver derivative chromosome: derivative chromosome leading to the deregulation of the pathological (onco)gene.

[b] In the rare cases with a 5'BCL2 breakpoint, the driver derivative chromosome of the t(14;18) is the der(18).

3.1. Classical FL

cFL is associated with a *BCL2* rearrangement in 85% of cases. It results from a t(14;18)(q32;q21) translocation that places the *BCL2* proto-oncogene under the transcriptional control of an IGH enhancer leading to BCL2 deregulation. Variant translocations involving immunoglobulin (IG) light chain genes (t(2;18)(p11;q21)/IGK::*BCL2*, t(18;22)(q21;q11)/IGL::*BCL2*)) are described in ~2% of cases [4]. Of note, *BCL2* rearrangements are also detected in 20 % of diffuse large B-cell lymphoma (DLBCL) and 2-3% of chronic lymphocytic leukemia (CLL) [5,6]. Recurrent additional chromosomal abnormalities (ACAs) include +X, +1q, +2p, +7, +8, +12q, +18/18q, del(1p), del(6q) and/or del(10q), leading to a complex hyperdiploid karyotype with frequent subclones [4]. Concomitant *BCL2* and *BCL6* (3q27) rearrangements are present in 10%, while *MYC* (8q24) rearrangement is detected in 2% of cFL [7].

FL lacking *BCL2* rearrangement are genetically heterogeneous showing either *BCL6* rearrangements, +1q, del(6q) and/or del(1)(p36), this latter abnormality targeting the *TNFRSF14* locus [8].

3.2. FL evolution

Gains of 3q, 8q, 12/12q, 18q and 21 are more frequently detected in transformed FL, as well as *MYC* rearrangement, loss of *CDKN2A, TP53* mutation and 2p16.1 amplification (including *REL* locus) [9,10].

Unusual FL lcases progressed to a very aggressive lymphoblastic TdT-positive proliferation with a *MYC* rearrangement [11].

3.3. Follicular large B-cell lymphoma

In FLBCL, the frequencies of *BCL6* rearrangement (40%) and *BCL2* rearrangement (13%) are different from cFL but similar to those described in DLBCL [12,13].

3.4. FL with uncommon features

The subtype 'FL with predominantly diffuse growth pattern' (dFL) also referred as '*BCL2*-R-negative, CD23 positive follicle center lymphoma' in ICC, is characterized by absence of *BCL2* rearrangement, presence of 1p36/*TNFRSF14* alteration, *STAT6* mutation and a favorable prognosis [2,14,15]. Arrays based single-nucleotide polymorphism (aSNP) analyses revealed a deletion or copy-neutral loss of heterozygosity (cnLOH) of 1p36.3 and 16p13.3 in 40% of cases [15]. Gains of 2/2q, 3/3q, 8q and 12q are also recurrent [14,15]. Mutations of both *CREBBP* and *STAT6* are frequent in dFL compared to cFL (74% vs 7%) [15].

3.5. Distinct related entities

Besides FL, two other distinct entities, namely duodenal type FL and *in situ* follicular neoplasms display a *BCL2* rearrangement. Conversely, pediatric-type FL (PTFL) and primary cutaneous follicular center lymphoma lack *BCL2* or *BCL6* rearrangements [2]. PTFL occurs as an isolated lymphadenopathy in children and young adults. Chromosomal microarray (CMA) analyses showed very few CAs including +7q, +15q, +16 and del(1p). *TNFRSF14* alterations are frequent (54%). Despite a high-grade morphology, the prognosis of PTFL is excellent with long-term remission after surgical excision [16].

3.6. Mutational profile

Numerous somatic mutations are described in FL, affecting genes involved in epigenetic deregulation (*KMT2D, CREBBP, EZH2, ARID1A, EP300*), transcriptional regulation (*MEF2B, BCL6*), BCR signaling (*CARD11*), JAK/STAT signaling (*SOCS1, STAT6, STAT3*), apoptosis negative control (*BCL2*) and immune evasion (*TNFRSF14, EPHA7*) [10].

3.7. Cytogenetic testing

Translocations involving *BCL2*/18q21 are easily detected by karyotype. When not performed, we recommend FISH using first BCL2, then BCL6 probes which may help in distinguishing FLBCL from cFL [2,13] (Table 2). In case of dFL or PTFL or cFL without *BCL2* and *BCL6* rearrangement, FISH testing using a TNFRSF14 probe (or CMA) is recommended [8,14,15]. Of note, within FLBCL cases without *BCL2* rearrangement, a strong expression of IRF4/MUM1 should lead to an IRF4 FISH analysis to exclude a large B-cell lymphoma with *IRF4* rearrangement (see below).

4. Mantle cell lymphoma

Mantle cell lymphomas (MCL) represent around 7% of all NHL. The non-nodal MCL (nnMCL) subgroup is characterized by leukemic presentation, splenomegaly, lack of SOX11 expression and indolent course, whereas the conventional MCL subgroup (cMCL) includes patients with SOX11-positive lymphadenopathies requiring initiation of treatment [1].

4.1. Cytogenetic profile

The t(11;14)(q13;q32)/IGH::*CCND1* translocation is detected in ~95% of cases and leads to CCND1 overexpression. Few cases display variant translocations t(2;11)(p11;q13)/IGK::*CCND1* or t(11;22)(q13;q11)/IGL::*CCND1* [17]. The t(11;14) can also be observed in multiple myeloma [18]. Cryptic *CCND1* rearrangements may occur resulting in false negative results using both CCND1 breakapart and IGH/CCND1 dual fusion probes. Some of these specifically involve the IG light-chain loci [19,20].

Non-random ACAs are present in 80% of MCL: del(1p), del(6q), del(8p), del(9p), del(9q), del(11q), del(13q)/-13, del(17p),+3q, +7p and +8q, leading to a complex karyotype (CK) in 60% of cases [21]. CK is defined by 4 or more CAs, including the t(11;14)) and confers reduced overall survival (OS) and treatment-free survival (TFS) [21–23]. The 17p/*TP53* deletion is significantly associated with CK or genomic complexity (GC) but does not impact outcome [21,24]. The co-occurrence of *TP53* alteration (mutation and/or deletion) with 9p21/*CDKN2A* deletion (~20% of cases) is correlated with a more

Table 2
Indications of cytogenetic analyses and recommendations for each disease.

Entity	Karyotype[a]	Mandatory (in bold) or recommended FISH probe analyses based on karyotype data	
		Abnormal karyotype consistent with the diagnosis	Normal karyotype or failure or not performed or diagnostic discrepancy
FL	Recommended	BCL2 or BCL6 MYC [b]	**BCL2** **BCL6** if *BCL2* not rearranged or FLBCL TNFRSF14 [c] if dFL or PTFL or BCL2 and BCL6 not rearranged
MCL	Mandatory if PB or BM infiltration [d]	IGH/CCND1 or CCND1, CCND2 [c] or CCND3, TP53, MYC, CDKN2A [b]	**IGH/CCND1 or CCND1** CCND2, CCND3, if *CCND1* not rearranged
SMZL	Mandatory if PB or BM infiltration	IGH (or BCL3 or PAX5), TP53 [b]	7q32 [c]
NMZL	Recommended		3q (BCL6), 18q (MALT1)
EMZL	Recommended	**if t(14;18): MALT1 and BCL2 if MALT1 not rearranged**	MALT1 or BIRC3/ MALT1, BCL2 **BIRC3/MALT1 or MALT1 in gastric localization**
B-PLL	Mandatory	MYC, TP53	
LPL/WM	Recommended	TP53	6q21/q23, cen4 [e], TP53
BL	Mandatory if PB or BM infiltration	MYC or IGH/MYC	**MYC, BCL2, BCL6** **IGH/MYC if *MYC* not rearranged**
GCB-DLBCL, and HGBL [f]	Recommended	**MYC** **IGH/MYC if *MYC* not rearranged** **BCL2 if *MYC* is rearranged** BCL6	
HG/LBCL-11q	Recommended	**11q23/11q24** [g,h]**, MYC, IGH/MYC**	
LBCL-IRF4	Recommended	**IRF4, MYC, BCL2** IGH if IRF4 negative	
PMBL	Recommended	CIITA [c]	PDL1-2 or JAK2 [h]

Abbreviations: FL, follicular lymphoma; FLBCL: follicular large B-cell lymphoma; dFL, diffuse FL; MCL, mantle cell lymphoma; LPL/WM, lymphoplasmacytic lymphomas/Waldenström macroglobulinemia; SMZL, splenic marginal zone lymphoma; NMZL, nodal marginal zone lymphoma; EMZL, extranodal marginal zone lymphoma; B-PLL, B-cell prolymphocytic leukemia; BL, Burkitt lymphoma; GCB-DLBCL, germinal centre B-cell diffuse large B-cell lymphoma; HGBL, High-grade B-cell lymphoma; HG/LBCL-11q, High-grade/ Large B-cell lymphoma with 11q aberration; LBCL-IRF4, large B-cell lymphoma with IRF4 rearrangement; PMBL, primary mediastinal B-cell lymphoma; PB, peripheral blood; BM, bone marrow.

[a] In case of BM, PB or fluid infiltration, karyotype is highly recommended or even mandatory

[b] Complementary FISH analyses are guided by karyotype results

[c] Non commercial FISH probes

[d] A fraction (less than 10%) of karyotypes is non-informative

[e] Potential chimeric probe: another probe on 4q can be used

[f] Extended FISH analyses are required in case of GCB-DLBCL and all HGBL to identify DLBCL/HGBL with *MYC* and *BCL2* rearrangements, and DLBCL with *MYC* and *BCL6* rearrangements.

[g] FISH analysis using the specific commercial probe 11q23/11q24 that targets both the 11q23.3 gain and the 11q24 deletion.

[h] Chromosomal microarray analysis for detecting unbalanced chromosomal abnormalities.

aggressive disease [22,25,26]. Tetraploid karyotypes, CK, *MYC*/8q24 rearrangements or chromothripsis are more commonly detected in the two morphological aggressive variants (blastoid and pleomorphic) [21,26,27].

The t(11;14) is isolated in a high proportion of nnMCL (75 %) while numerous ACAs or chromothripsis are observed in cMCL [21,28]. Among patients with nnMCL, CK also predicts a shorter time to first treatment [21,26]. Of note, *TP53* alterations are distributed in similar frequencies in cMCL and nnMCL (37%) [26].

MCL CCND1-negative (<5%) is genetically characterized by juxtaposition of IG enhancers to *CCND2* (12p13) in about two-third of cases, or *CCND3* (6p21). The *CCND2* rearrangement predominantly involves the IGK locus [29,30]. Most of *CCND3* and some *CCND2* rearrangements result from a cryptic insertion of IGK (or IGL) enhancer elements that are juxtaposed near to the *CCND3* or *CCND2* genes [30].

4.2. Mutational profile

Recurrent somatic mutations in MCL include *ATM, CCND1, TP53, BIRC3, KMT2D, CDKN2A* and *RB1* genes [28]. *TP53* mutations are associated with poor response to immunochemotherapy and short OS [24].

4.3. Cytogenetic testing

Translocations involving the CCND gene family are easily detectable by chromosome banding analysis (CBA) except for the cryptic t(12;14)(p13;q32)/IGH::*CCND2*. Therefore, we consider karyotyping as mandatory in case of peripheral blood (PB) or bone marrow (BM) infiltration (Table 2). When there is no informative karyotype, interphase FISH testing using a CCND1 (or IGH/CCND1) probe is required. We recommend using an extensive FISH panel targeting *CCND2* and *CCND3* if a CCND1-negative MCL is suspected. Some cases are not detectable by commercial or custom breakapart FISH probes [30,31]. Those cases require additional cytogenetic and/or molecular investigations (such as FISH targeting IGK and IGL enhancer regions, or whole genome sequencing) to identify cryptic or atypical *CCND1, CCND2* or *CCND3* rearrangements [19,20,30].

5. Marginal zone lymphomas

The marginal zone lymphomas (MZL) family in WHO-HAEM5 includes extranodal MZL of mucosa-associated lymphoid tissue (EMZL), nodal MZL (NMZL), pediatric nodal MZL and primary cutaneous MZL (PCMZL). Splenic marginal zone lymphoma (SMZL) is now classified in the splenic B-cell lymphoma group [1].

All these entities share some cytogenetic characteristics as +3/3q and/or +18/18q, +1q, +8q, +12q and del(6q). The association +3/+18 occurs in ~20% of cases and is characteristic of MZL.

5.1. EMZL

Four recurrent translocations are the hallmark of EMZL, with variable frequencies according to the involved anatomic site [32–35].

5.1.1. t(11;18)(q22;q21)/BIRC3::MALT1

This fusion transcript is mainly detected in pulmonary (30-50%), intestinal (10-60%) and gastric (5-25%) EMZL. In gastric EMZL, it is more frequent in *Helicobacter pylori* (HP)-negative forms. Importantly, the t(11;18) is associated with a lack of durable tumor-response to HP antibiotics therapy. Conversely, the t(11;18) is rarely found in EMZL from the salivary gland (1%) and is absent in those from the thyroid, skin and liver.

5.1.2. t(1;14)(p22;q32)/IGH::BCL10

This extremely rare alteration leading to an upregulation of *BCL10* is predominantly observed in pulmonary (9%) or intestinal (4%) EMZL.

5.1.3. t(14;18)(q32;q21)/IGH::MALT1

This translocation, leading to *MALT1* deregulation is mainly described in lesion of ocular adnexa/orbit (~25%) and salivary glands (16%). It must not be confused with the t(14;18) of FL, which involves

BCL2 located about 4.3Mb telomeric to *MALT1*.

5.1.4. t(3;14)(p14.1;q32)/IGH::FOXP1

It is most commonly found in thyroid (50%) and ocular adnexa/orbit (10~20%) EMZL. Its detection is extremely useful for the differential diagnosis with other thyroid disorders, particularly FL.

5.2. SMZL

Typical translocations of EMZL are not detected in SMZL. The predominant CAs are del(7q), del(6q), +3/3q, +12q, and translocations involving 8q/1q/14q [36]. CK (3 or more CAs) are common (50-60%) but their prognostic significance remains unclear.

Interestingly, the detection of del(7q) may help the differential diagnosis with Waldenström macroglobulinemia. The del(7q) comprises the 7q32 band with a minimal deleted region of 2.8 Mb [37].

Three rare translocations, t(9;14)(p13;q32)/IGH::*PAX5,* t(14;19)(q32;q13)/IGH::*BCL3* and t(2;7)(p11;q21)/IGK::*CDK6,* have been reported in SMZL, but also in CLL and DLBCL [36,38]. Despite a high prevalence of 17p/*TP53* deletion, cases with t(2;7) or variants involving *CDK6* are associated with an indolent outcome [38].

5.3. PCMZL

Approximately 10% to 20% of PCMZL harbor t(14;18)(q32;q21)/IGH::*MALT1*, t(11;18)(q22;q21)/*BIRC3::MALT1* and t(3;14)(p14;q32)/IGH::*FOXP1* [39].

5.4. NMZL

No recurrent translocations or gene fusions are described. The most frequent CAs are +3/3q, +18/18q and del(6q) [35]. Deletion 1p,+6p, +1q and +12q are less frequently detected [35,40,41].

5.5. Pediatric nodal marginal zone lymphoma

Pediatric nodal marginal zone lymphoma (PNMZL) is a rare indolent B-cell NHL that occurs predominantly as a localized lymphadenopathy in children and adolescents. PNMZL displays a very low GC, trisomy 3 or 18 being exceptionally observed. The cnLOH including the *TNFRSF14* gene is the most frequent cytogenomic abnormality followed by focal 3q gain, partial trisomy 11 and +12p [42].

5.6. Mutational profile

Somatic variants of *KMT2D, PTPRD, NOTCH2, KLF2* and *BRAF* are frequent in NMZL but not in EMZL with the exception of pulmonary and ocular EMZL which display recurrent mutations of *KMT2D* [43]. In addition, mutational profiles are significantly different depending on the anatomical location - *e.g.* mutations in NF-kB pathway in ocular adnexal or gastric and *TET2* mutations in thyroid EMZL [44]. In contrast, SMZL share with NMZL a common molecular profile, *KLF2* and *NOTCH2* being the more frequent mutations [43]. In contrast to adult NMZL but similar to PTFL, the most frequently mutated genes in PNMZL are *TNFRSF14, MAP2K1* and *IRF8* [42,45,46].

5.7. Cytogenetic testing

Due to the strong diagnostic impact of karyotype among small B-cell NHL, we consider CBA as mandatory for MZL, in case of PB or BM infiltration. The identification of t(11;18) using specific FISH probes (MALT1 or BIRC3/MALT1) is required in gastric forms of EMZL (Table 2). In case of t(14;18), FISH using MALT1 and/or BCL2 probes may be useful to distinguish EMZL from FL.

6. Splenic diffuse red pulp small B-cell lymphoma

Splenic diffuse red pulp small B-cell lymphoma (SDRPL) is an uncommon leukemic lymphoma with involvement of the splenic red pulp by small B-lymphocytes, usually with a villous cytology. Non-specific CAs are detected in one-third of SDRPL cases. Translocation t(9;14)(p13;q32)/IGH::*PAX5*, del(17p), del(7q), +18 and +3 have been reported [47]. *CCND3* and *BCOR* mutations are present in 21-24% of cases, whereas *NOTCH2* and $BRAF^{V600E}$ mutations are very rare [48].

7. Hairy cell leukemia

No specific CA is described for Hairy cell leukemia (HCL); +5 is the most frequent CA, followed by del(6q) and del(7q) [49]. HCL has distinct immunophenotypic and molecular profile with $BRAF^{V600E}$ somatic mutation in ≥95% of cases. Contrary to the other splenic B-cell lymphomas, cytogenetic analysis is not used for HCL diagnosis.

8. B-cell prolymphocytic leukemia

B-cell prolymphocytic leukemia (B-PLL) is no longer considered as an entity in WHO-HAEM5. But according to the ICC [2] and the GFCH B-PLL study [50,51], the GFCH still considers the B-PLL as an independent entity. B-PLL is a very rare disease occurring in elderly people. The previous WHO classifications recognized the B-PLL as a distinct entity characterized by the presence of prolymphocytes in more than 55% of the lymphoid cells in PB. This definition excluded prolymphocytic progression of CLL and atypical leukemic forms of MCL (see above). The clinical evolution is generally aggressive, but a subgroup of patients has a more indolent course.

8.1. Cytogenetic profile

The karyotype is complex (≥3 CAs) in three-quarters of patients and highly complex (≥5 CAs) in half of cases. The most frequent CA is a IG::*MYC* translocation (62%). *MYC* gain/amplification (~15% of cases) is mainly subclonal and overlooked as part of a CK. Deletion 17p, often associated with *TP53* mutation, is also frequent (38%). The other recurrent CAs are +3, +12, +18, del(8p) and del(13q) [50,52,53]. A prognostic classification has been proposed, with three cytogenetic risk groups: low-risk (no *MYC* aberration), intermediate-risk (*MYC* aberration but no del(17p)), and high-risk (*MYC* aberration and del(17p)) [50].

8.2. Mutational profile

The most frequently mutated genes are *TP53, MYD88, BCOR, MYC, SF3B1, SETD2, CHD2, CXCR4*, and *BCLAF1* [50].

8.3. Cytogenetic testing

The karyotype is mandatory for differential diagnosis with other mature B-cell NHL, especially MCL. We additionally recommend performing MYC and TP53 probes to identify *MYC* aberrations and del (17p), the two key prognostic CAs of B-PLL that might not be detected within a CK.

9. Lymphoplasmacytic lymphomas: Waldenström macroglobulinemia and IgM monoclonal gammopathy of undetermined significance

Waldenström macroglobulinemia (WM) is the most common subtype of lymphoplasmacytic lymphomas (LPL) (WHO-HAEM5). WM is characterized by the presence of serum monoclonal IgM with BM infiltration by lymphoplasmacytic cells [1].

9.1. Cytogenetic profile of WM

A median of three CAs are described in WM [54–56]. A CK (≥3 CAs) is observed in about 15% of WM cases, including highly (H) CK (≥5 CAs) [54]. The most frequent CAs include del(6q), del(13q), +18, +4, del (17p), +12, +3 and del(11q) [54,57,58]. There are at least two minimal deleted regions located on 6q21 and 6q23, including *PRDM1* and *TNFAIP3* respectively; del(13q) affects the micro RNAs *MIR15A* and *MIR16-1* (13q14); 17p13 and 11q22 deletions include *TP53* and *ATM* respectively [55]. Using array-CGH or whole exome sequencing, the 6p gain (6p12-6p25) has also been described in WM [55,59]. Although not specific, del(6q) and +4 are helpful diagnostic biomarkers, considering the high frequency (20-40%) of del(6q) in WM and the rarity of +4 in other B-cell mature disorders. Del(6q), *TP53* disruption and HCK are associated with short PFS and OS [54,60].

9.2. Mutational profile of WM

MYD88^{L265P} is the hallmark driver mutation found in more than 90% of WM; *CXCR4* mutations are also observed in up to 40% of cases, usually concurrent with *MYD88*. Other mutations have been described at a lower frequency in *ARID1A, CD79B, SPI1* or *TP53* genes, the last two mutations being associated with poor survival [61]. The *TP53* mutations are highly correlated to del(17p) [60].

9.3. IgM monoclonal gammopathy of undetermined significance

IgM monoclonal gammopathy of undetermined significance (IgM-MGUS) is an individualized entity belonging to monoclonal gammopathies in the WHO-HAEM5 [1]. It is considered as a pre-malignant condition for multiple B-cell NHL, most notably for WM. The frequency of patients displaying CNAs progressively increases from IgM-MGUS (36%) to smoldering (73%) and symptomatic (82%) WM. The del(6q) and +18 are rare (<5%) in IgM-MGUS, while +4 and +12 are absent [56]. The *MYD88*^{L265P} mutation is observed in 50% of cases [62].

9.4. Cytogenetic testing in LPL

The karyotype is recommended in LPL, but given the generally low level of BM (or PB) infiltration, is not always informative despite the use of oligonucleotide CpG with interleukin 2 (ODN-CpG + IL2). Therefore, in case of normal karyotype, FISH analyses with 6q21/6q23 and 4q probes are useful to distinguish LPL/WM from other B-cell mature malignancies, especially SMZL. Use of TP53 probe is also recommended to detect a del(17p); but due to the low level of BM infiltration, tumor cell sorting could be of interest.

10. Non-Chronic lymphocytic leukemia/Small Lymphocytic Lymphoma Monoclonal B-cell Lymphocytosis

Non-Chronic lymphocytic leukemia/Small Lymphocytic Lymphoma Monoclonal B-cell Lymphocytosis (non-CLL/SLL MBL) corresponds to any clonal B-cell expansion without the typical CLL/SLL phenotype, with no symptoms or diagnostic criteria of another mature B-cell neoplasm [1]. The majority of cases have features consistent with a marginal zone origin. In these cases, CK, del(7q), translocations involving 7q including the t(2;7)(p11;q21)/IGK*::CDK6*, and i(17)(q10) are reported [63]. Mutations in genes involved in marginal zone differentiation (i.e. *NOTCH2, MYD88, TNFAIP3* and *CD79B*) occur in 1/3 of cases [64]. If a non-CLL/SLL clone is present, it is important to exclude an underlying lymphoma. When PB infiltration is sufficient, a molecular testing (e.g. *MYD88*) and karyotype/FISH analyses (to exclude MCL) should be performed.

11. Burkitt lymphoma

Burkitt lymphoma (BL), the most frequent pediatric B-cell NHL accounts for approximately 3% of adult's lymphomas [65].

11.1. Cytogenetic profile

Although not specific, IG::*MYC* translocations defines BL and constitutes the hallmark of this disease. It is the primary genetic event leading to juxtaposition of an IG enhancer to the *MYC* oncogene, resulting in its deregulation. Of note, the 8q24 breakpoints are scattered up to 350 Kb upstream and 650 Kb downstream to the *MYC* locus [66].

The IG::*MYC* rearrangement is associated with additional CAs in ~60% of BL karyotypes [67]. Recurrent ACAs are +1q, +7, +12, +21, del(6q), der(13q) and del(17p). Minimal critical regions have been described for +1q (mostly 1q21.1-q25.1), +7q (7q21.1-qter) and del (6q) (6q24.1-qter) [68]. A simple karyotype defined as a maximum of 3 ACAs in addition to the IG::*MYC* rearrangement is a strong diagnostic marker. Nonetheless, GC could occur at disease progression or relapse [65].

11.2. Mutational profile

It is now recommended to distinguish two subtypes: EBV-positive and EBV-negative BL [1]. EBV-positive cases show fewer driver mutations (*GNA13, FOXO1*), compared with EBV-negative cases (*TCF3, ID3* and *CCND3*) [69].

11.3. Cytogenetic testing

As CBA identifies both the IG::*MYC* translocation and the simple karyotype, it is mandatory in case of PB or BM infiltration (Table 2).

The use of a wide-gap MYC probe is required in order to cover all the putative *MYC*/8q24 breakpoints. Rare cryptic insertions (2%) of *MYC* into the IGH locus (or conversely) lead to a normal profile with the MYC breakapart probe, justifying an additional dual fusion IGH/MYC probe [66]. Both *MYC* translocations with a non-IG partner and *BCL2* or *BCL6* rearrangement should lead to exclusion of the diagnosis of BL [1]. Therefore, a full FISH strategy using MYC, IG/MYC, BCL2 and BCL6 probes is often needed to distinguish BL from other high-grade B-cell lymphomas (Fig. 1). Metaphase FISH analysis is particularly helpful in these situations.

12. Diffuse large B-cell lymphoma, not otherwise specified

DLBCL, not otherwise specified (DLBCL, NOS) accounts for one-third of NHL cases in adults and 10% in children's. Gene expression profile has revealed two major molecular subtypes based on their cell of origin: the germinal center B-cell-like DLBCL (GCB-DLBCL) and the activated B-cell-like DLBCL (ABC-DLBCL), the latter being associated with a worse prognosis [1]. The Hans' immunohistochemical algorithm is widely used in routine practice to distinguish them [70].

12.1. Cytogenetic profile

DLBCL exhibits numerous CAs: del(6q), +18q, +X, +1q, +2p, +3/+3q, +7, +12/+12q, -Y, +5, +6p, +8q, del(10q), +11/+11q, del(17p) resulting in CK [71,72]. Single rearrangements involving *BCL6* (3q27), *BCL2* (18q21) or *MYC* (8q24) are detected in ~30%, 15-20% and 8%, respectively [5,73,74].

Overall, IG rearrangements targeting *BCL2, BCL6* or *MYC* involve predominantly the IGH locus. While *BCL2* is invariably rearranged with an IG locus, non-IG partners are detected for *MYC* and *BCL6* translocations in 50% and 60%, respectively [75,76]. The non-IG::*BCL6* translocations include more than 45 distinct partner genes, *IKZF1*/7p12 being one of the most common. Regarding *MYC* rearrangements,

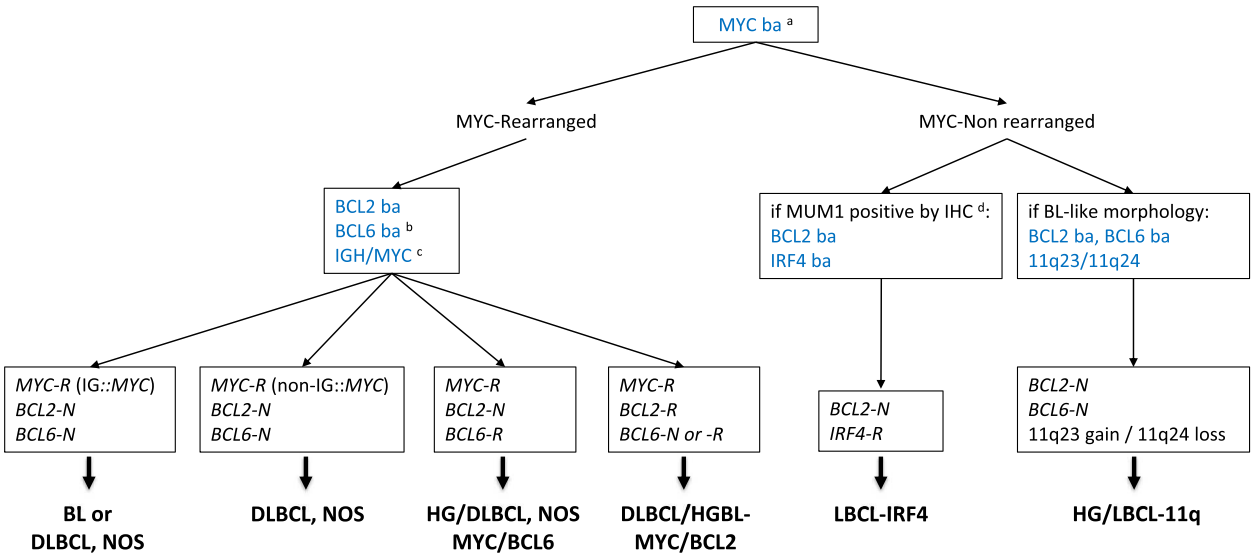

Fig. 1. FISH diagnostic strategy in aggressive B-cell lymphomas.
FISH probes in blue; ba breakapart, -N normal, -R rearranged, IHC immunohistochemistry
[a]A IGH/MYC double fusion probe is recommended to overcome the false negative cases if using MYC ba probe only
[b]could be performed only if *BCL2-N*
[c]IGK and IGL to confirm the IGK::*MYC* or IGL::*MYC* rearrangement in case of IGH::*MYC* negative
[d]MUM1 strongly positive or aberrant immunophenotype CD10+/BCL6+/MUM1+

numerous non-IG partner genes are reported: *BCL11A*/2p16, *IKZF1*/7p12 and *PAX5*/9p13 are the most frequent [77]. The clinical relevance of the *MYC* partner genes (IG vs non-IG) remains currently controversial [74,78]. In addition, the prognostic impact of *BCL2, BCL6* and *MYC* extra-copies is not established [73,79].

Some CAs are not randomly distributed; +2p, +7q, +12q and to lesser extent +1q are preferentially identified in GCB-DLBCL whereas ABC-DLBCL are enriched in +3/+3q, +18/+18q21 (*BCL2*), +19q13 (*SPIB*), del(6q) and focal del(9p21) (*CDKN2A*) [72]. Remarkably, IG::*BCL2* rearrangements occur exclusively in GCB-DLBCL while the t(3;14)(q27;q32)/IGH::*BCL6* is associated with ABC-DLBCL [5,72]. Conversely, a single *MYC* rearrangement (without *BCL2* or *BCL6* rearrangement) is equally distributed in both GCB-DLBCL and ABC-DLBCL [5]. In addition, the cytogenetic signature of DLBCL with IG::*BCL2* rearrangement is similar to FL suggesting their putative common cell of origin [72]. Similarly to FL, concomitant *BCL2/BCL6* rearrangements occur in 5% of DLBCL [79].

12.2. Mutational profile

The GCB-DLBCL and ABC-DLBCL subtypes share somatic mutations targeting epigenetic remodeling (*KMT2D, CREBBP/EP300*), immune surveillance (*B2M, CD58, CIITA*), DNA damage (*TP53*), BCL6 regulation (*MEF2B*) and B-cell differentiation (*FOXO1*). The *GNA13, EZH2, TNFRSF14, BCL6, S1PR2* and *ARHGEF1* mutations preferentially segregate to GCB-DLBCL subtype. In contrast, ABC-DLBCL is enriched in somatic mutations that activate the NFκB pathway (*MYD88, CD79B, TFNAIP3, CARD11*) and block B-cell differentiation (*PRDM1*) [80].

Recent genomic integrative studies have led to a new molecular subclassification of DLBCL, NOS based on a combination of cytogenetic and molecular alterations. Five to seven genetic subgroups are identified, each defined by a given pattern of genetic features and distinct outcomes. Interestingly, recurrent translocations involving *BCL2, BCL6, MYC* as well as *TP53* deletions, +18q21 and GC are an integral part of this classification [81].

The cytogenetic testing strategy of DLBCL, NOS is detailed in the following section.

13. Diffuse large B-cell lymphoma/High-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements

The WHO-HAEM5 reassigned aggressive B-cell lymphomas harboring dual *MYC* and *BCL2* rearrangements in the category now referred as "Diffuse large B-cell lymphoma/High-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements" (DLBCL/HGBL-MYC/BCL2) [1]. The presence of a dual rearrangement of *MYC* and *BCL6* is now excluded from this category (see below).

DLBCL/HGBL-MYC/BCL2 is a rare but very aggressive disease accounting for approximatively 7% of DLBCL and 50% of HGBL [5,82]. DLBCL/HGBL-MYC/BCL2 (formerly called "double-hit" lymphoma) encompasses both rare cases with a triple rearrangement *MYC/BCL2/BCL6* and mature LBCL arising from a transformation of FL-t(14;18)-positive [83,84].

DLBCL/HGBL-MYC/BCL2 is associated with the worst prognosis among aggressive B-cell lymphomas and needs a more intensive therapeutic approach.

13.1. Cytogenetic profile

The karyotype is often highly complex (mean of 8 CAs) with mostly +X, del(6q), +7, +8 or +12/+12q [85]. The most frequent pattern consists of association of t(14;18)(q32;q21)/IGH::*BCL2* with t(8;14)(q24;q32)/IGH::*MYC*. *MYC* can also be rearranged with IGL or IGK loci and less frequently by a non-IG::*MYC* translocation [74,82]. About half of the triple rearrangements (*MYC/BCL2/BCL6*) exhibits a t(3;8)(q27;q24)/*BCL6::MYC*, leading to overexpression of *MYC* by *BCL6* enhancer elements [86,87].

Several studies show a negative prognostic impact of a dual *BCL2/MYC* rearrangement only in case of IG::*MYC* rearrangements, suggesting the relevance of determination of the *MYC* partner gene [74,78,84].

13.2. Mutational profile

DLBCL/HGBL-MYC/BCL2 harbor mutations reported both in GCB-DLBCL (*CREBBP, KMT2D, EZH2, BCL2, FOXO1, GNA13* and/or *TNFRSF14*) and in BL (*TP53, MYC, ARID1A* and *CCND3*). The *CCND3*

locus seems to be frequently mutated in triple-hit DLBCL [83,84].

13.3. Cytogenetic testing

The karyotype of DLBCL, NOS and DLBCL/HGBL-MYC/BCL2 has the advantage of detecting both recurrent translocations, CK and CAs associated to GCB-DLBCL or ABC-DLBCL. We recommend performing interphase FISH using MYC breakapart and IGH/MYC dual fusion probes in all GCB-DLBCL and HGBL [88,89], not only in the double-expressor BCL2+/MYC+ DLBCL and/or tumors with a high proliferation index [5]. In case of *MYC* rearrangement, FISH using a BCL2 probe is required to identify DLBCL/HGBL-MYC/BCL2 but a full screening with also a BCL6 probe is the best strategy to distinguish DLBCL/HGBL-MYC/BCL2 (including triple hit cases) from DLBCL-MYC/BCL6 or DLBCL, NOS (Fig. 1). When available, metaphase FISH is of great interest, particularly to identify cryptic rearrangements [88,89].

14. High-grade/Diffuse large B-cell lymphoma, NOS with *MYC* and *BCL6* rearrangements

An important change in WHO-HAEM5 is the distinction of 'DLBCL, NOS with *MYC* and *BCL6* rearrangements' that lack a *BCL2* rearrangement [1]. The ICC considers the 'HGBL with *MYC* and *BCL6* rearrangements' as a new provisional entity [2].

High-grade/Diffuse large B-cell lymphoma, NOS with MYC and BCL6 rearrangements (HG/DLBCL, NOS-MYC/BCL6) represents a rare form of DLBCL (<2%) with a female predominance whose prognosis remains controversial. The tumor phenotypes are equally distributed in GCB-DLBCL and non-GCB-DLBCL subtype [79,83,84,88].

14.1. Cytogenetic profile

Karyotype is mainly complex (80%), with no single profile clearly emerging [90]. The special pattern of t(3;8)(q27;q24)*/BCL6::MYC* sometimes referred as "pseudo double-hit" occurs in 30% of cases [86].

14.2. Mutational profile

HG/DLBCL, NOS-MYC/BCL6 share somatic mutations with DLBCL/HGBL-MYC/BCL2 including *KMT2D, FOXO1, TNFRSF14, ARID1A, MYC* and *CCND3*. Interestingly, a subgroup displaying a non-GCB phenotype exhibits mutations of *MYD88, CD79B* and *NOTCH2*, suggesting its common cell of origin with MZL. In contrast to DLBCL/HGBL-MYC/BCL2, *TP53* is less frequently mutated [83,84].

14.3. Cytogenetic testing

We recommend performing FISH analyses for *BCL2* and *BCL6* in all cases of DLBCL or HGBL that exhibit a *MYC* rearrangement (Fig. 1). Again, karyotype is very useful to identify these specific cases.

15. High-grade/Large B-cell lymphoma with 11q aberration

High-grade/Large B-cell lymphoma with 11q aberration (HG/LBCL-11q) is now recognized in WHO-HAEM5 as a defined entity but still referred as a provisional entity according to the ICC [1,2]. HG/LBCL-11q is morphologically close to BL, mainly affects children's and young adults, and has a favorable prognosis [91,92].

15.1. Cytogenetic profile

HG/LBCL-11q is genetically characterized by a proximal gain and a distal loss of chromosome 11q. Two minimal regions of gain are described: 11q22.3-q23.1 and 11q23.3, with some cases harboring 11q23.3 amplification [91,93]. The most specific abnormality is the 11q24.3-q25 loss encompassing *FLI1, NFKB* and *ETS1* genes, associated with a 11q23 gain. Some cases exhibit a cnLOH of 11q24 associated with the prototypical 11q23.3 gain while others have a 11q24 loss alone [91,94,95]. The 11q23 gain/11q24 loss pattern can also be seen in BLs or other HGBLs (Table 3) [95–98].

There are three main patterns: large 11q13.4-23.3 duplication/inversion (dup/inv), shorter dup/inv/del and simple dup/del [95]. The karyotype could be more complex than in BL including mostly del(6q) and +12 [91,93]. Using aSNP, the most frequent ACAs are +12q, +5q, del(7q), del(6q) and del(13q) [91,94].

15.2. Mutational profile

The mutational spectrum is similar to the one described in GCB-DLBCL or HGBL, including *BTG2, DDX3X, ETS1, EP300*, and *GNA13* alterations but lacks the characteristic BL mutations of the ID3-TCF3 axis or the Swi/Snf complex [91,94].

15.3. Cytogenetic testing

FISH using appropriate 11q probes (targeting the 11q23.3 and 11q24 regions) or CMA are required to diagnose a HGBL-11q, together with FISH analyses to exclude *MYC, BCL2* and *BCL6* rearrangements (Fig. 1) [2,96].

16. Large B-cell lymphoma with *IRF4* rearrangement

Large B-cell lymphoma with *IRF4* rearrangement (LBCL-IRF4) is rare, accounting for 20% of pediatric FLBCL/DLBCL but less than 5% in adults [92,99]. LBCL-IRF4 is defined by a *IRF4(MUM1)*/6p25 rearrangement resulting in MUM1 increased expression. LBCL-IRF4 presents mainly with a cervical lymph node or a gastrointestinal tract involvement [92]. The tumor shows a FLBCL and/or a DLBCL morphology with either a GCB phenotype, mainly in children and young adults, or a non-GCB phenotype. In adults, 20% of DLBCL with an atypical immunophenotype CD10+/BCL6+/MUM1+ harbor an isolated *IRF4* rearrangement [100]. Children and young adults exhibit an excellent prognosis whereas the outcome of older patients remains currently unknown [92,100].

16.1. Cytogenetic profile

LBCL-IRF4 mainly involves a cryptic t(6;14)(p25;q32)/IGH::*IRF4* (80%), while IGL and IGK are involved in the remaining cases. While CMAs show few ACAs with frequent del(17p)*/TP53*, +7 and +11q in children or young adults, GC is observed in older patients with higher frequency of del(17p)*/TP53*, +18q or del(6q) [99,100].

16.2. Mutational profile

Next generation sequencing revealed frequent somatic mutations of *IRF4* (80%), NFκB related genes (*CARD11, CD79B, MYD88*) and in intron 1 of *BCL6* (50%), with a global higher mutation load in elderly patients [100,101].

16.3. Cytogenetic testing

As IG::*IRF4* rearrangements are not detectable by CBA, FISH using an IRF4 breakapart probe is mandatory when the diagnosis is oriented towards MUM1-positive FLBCL or CD10+/BCL6+/MUM1+ DLBCL (Table 2). The absence of *MYC* and *BCL2* rearrangements is required to confirm the diagnosis of LBCL-IRF4 (Table 3, Fig. 1).

When there are strong arguments for a LBCL-IRF4 but no *IRF4* rearrangement, FISH using an IGH probe can detect an IGH insertion at 6p25 suggesting a IGH::*IRF4* rearrangement. In addition, the presence of a *IRF4* mutation could be considered as a surrogate diagnostic marker.

Table 3
Distribution and frequency of cytogenetic abnormalities in aggressive B-cell lymphomas (excluding primary mediastinal B-cell lymphoma).

Entities	Karyotype	MYC rearrangement	BCL2 rearrangement	BCL6 rearrangement	IRF4 rearrangement	11q23 gain/ 11q24 loss d	References
BL	Simple [a]	100% Always IG::*MYC*	No	No	No	Rare	[1,67,92,98]
DLBCL, NOS	Complex	8-12%	15-20%	30%	Rare [b]	Rare	[1,5,71,75,100,101]
DLBCL/HGBL-MYC/BCL2	Complex	100% : 60% IG::*MYC* 40% non-IG::*MYC*	100%, mostly IGH::*BCL2*	10-15%	Rare [c]	Rare	[1,2,74,96]
HG/DLBCL, NOS-*MYC/BCL6*	Complex	100% 30% *BCL6::MYC*	No	100% 30% *BCL6::MYC*	Unknown	Rare	[1,2,75,77,97]
HG/LBCL-11q	Complex	No	No	No	No	100% [d,e]	[92,93]
LBCL-*IRF4*	Unknown	No	No	~10%	100% [c]	No	[1,92,100,101]

DLBCL: Diffuse large B-cell lymphoma; NOS: Not otherwise specified; HGBL: High-grade B-cell lymphoma; LBCL: large B-cell lymphoma.
[a] Simple karyotype if less than 4 abnormalities including the IG::*MYC* translocation, complex karyotype otherwise
[b] Only if a *IRF4* rearrangement coexists with a *BCL2* and/or a *BCL6* rearrangement
[c] The FISH using a breakapart IRF4 probe is negative in about 10% of cases
[d] Only if confirmed by appropriate FISH probes targeting 11q23 and 11q24, or by chromosomal microarray analysis
[e] A single pattern of 11q24 loss or 11q23 gain together with 11q24 cnLOH is also described

17. Primary mediastinal large B-cell lymphoma

Primary mediastinal large B-cell lymphoma (PMBL) is an aggressive subtype of NHL of presumed thymic B-cell origin, accounting for ~10% of LBCL with a predominance of young females [1].

17.1. Cytogenetic profile

By CMA analyses, the most frequent CNA is +9p24.1 (70%) including a cluster of three genes (*JAK2, CD274/PDL1* and *PDCD1LG2/PDL2*) [102,103]. Other recurring CNAs include +2p, +Xp, +12q, +Xq, +9q, +8q, +7q, +5p and del(6q). Focal amplifications of 9p24/*JAK2-PDL1-PDL2* and 2p16/*REL* are observed in 29% and 14% of cases, respectively. PMBL is also characterized by a high prevalence of cnLOH targeting chromosomes 6p, 15q and 17q [103]. Rearrangements targeting *PDL1* or *PDL2* are also found in ~20% of PMBL and involve numerous partner genes/loci (IGH, IGL, *JAK2, CIITA, PHACTR4, N4BP2, EEF1A1, CLDN14*) [104,105]. Both rearrangements and genomic gains of *PD-L1/PD-L2* loci lead to overexpression of the PDL1 and PDL2 proteins thus impairing T-cell-mediated immune response [104]. The *CIITA* gene (16p13) is disrupted by chromosomal translocations (11-38%), deletions and somatic mutations, all leading to a non-functional CIITA protein [106,107].

17.2. Mutational profile

PMBL includes somatic mutations that contribute to escape the immune surveillance (*PDL1, PDL2, CIITA, CD58, B2M*), activate the NFκB and JAK-STAT pathways (*SOCS1, RELB, TNFAIP3, JAK1, STAT6*) and affect the interferon regulatory response (*IRF4, IRF8, IRF2BP2*) or the DNA damage (*TP53*) [107,108].

17.3. Cytogenetic testing

FISH using PDL1-PDL2 or JAK2 probes may help to diagnose PMBL. CMA appears also to be a method of choice in order to identify characteristic CNAs (Table 2).

18. Recommendations

Table 2 summarizes the required or recommended cytogenetic tests for each disease. Overall, karyotype is highly recommended (or mandatory) when infiltrated samples are available. Karyotype remains effective when tumor infiltration is low in indolent but also in aggressive lymphomas. Metaphase FISH allows to accurately identify and localize cryptic insertions of major oncogenes (*MYC, BCL2, CCND1*) or regulatory sequences of IG loci. CBA or CMA should be combined to FISH in the majority of situations tor detect the classifying abnormalities.

Regarding aggressive B-cell lymphomas or DLBCL, FISH has become crucial in the diagnostic approach to discriminate between BL, DLBCL/HGBL-MYC/BCL2, DLBCL, NOS or other infrequent genetic subtypes (Table 3). A rapid diagnostic orientation can be achieved through an extensive panel of FISH probes (MYC, IGH/MYC, BCL2 and BCL6), which could be performed either simultaneously or sequentially. We propose a sequential strategy of FISH analyses that helps diagnosis and may resolve challenging situations (Fig. 1). We suggest to include the use of IGH/MYC double fusion probe in order to avoid the false negative cases (2-5%) described using a single MYC breakapart probe [88,89].

19. Technical aspects

CBA remain easy to perform in the majority of indolent and small B-cell lymphomas as well as any other lymphomas with BM, PB or fluid infiltration. In contrast, the most aggressive B-cell lymphomas present lymph nodes or tissue invasion. The need of fresh material has hampered the routine use of CBA from a solid tissue specimen. Indeed, karyotyping from solid tissue requires a dedicated circuit for ensuring aseptically non-fixed biopsies or lymph node resections. After a mechanical dilacerating, the cell culture is carried out with a higher concentration than for PB or BM samples (Table 4). Overall, a short culture (<24h or even less for BL) is preferable for LBCLs or highly proliferative diseases, while a long culture (72h) with mitogens is indicated for low grade B-cell lymphomas (Table 4). Indeed, the use of ODN-CpG + IL2 have demonstrated its capacity to induce tumor cell division in MCL, MZL, WM and B-PLL [21,38,50,58]. In the case of limited material, a unique short culture without mitogens is appropriate in children (where HGBL and LBCL predominate) and adults under 50 years of age.

FISH can be performed on metaphases, thereby allowing the detection of cryptic rearrangements. The choice of FISH probes is guided by the referral indication together with morphological data and/or karyotype (Table 2). Interphase FISH is also widely used as a standalone test performed on formalin fixed paraffin-embedded specimens, frozen tissue sections, touch preparations or smears. Importantly, after tissue sectioning (very thin section <4 μm), a pre-checking step of infiltration and localization of tumor cells is mandatory. The use of split probes, which are easier to interpret and generally sufficient for identification of recurrent rearrangements, is recommended for tissue FISH. Caution should be taken in case of *in situ* neoplasia (i.e. *in situ* follicular neoplasia or *in situ* mantle cell neoplasia) where the lymphoma cells are restricted to small area.

Table 4
Management of samples: optimal conditions, times of cell culture and cell concentrations.

Suspected diagnosis	Culture time and specifications	Cell concentration for bone marrow and peripheral blood	Cell concentration for tissue sample and fluid [a,b]
Small B-cell lymphomas (except FL)	Long culture with ODN-CpG + IL2: 72h[c]	1 to 2 M/ml	2 M/ml
Unspecified	Short culture without mitogens: 17 to 24h	1 to 2 M/ml	3 to 5 M/ml
	Long culture with ODN-CpG + IL2: 72h[c]		2 M/ml
BL, HGBL	Very short culture without mitogens: 2 to 17h	2 M/ml	3 to 5 M/ml
Large B-cell lymphomas or FL	Short culture without mitogens: 17 to 24h	2 M/ml	3 to 5 M/ml
B-PLL	Long culture with ODN-CpG + IL2: 72h[c]	1 to 2 M/ml	

FL: follicular lymphoma; BL: Burkitt lymphoma; HGBL: high-grade B-cell lymphoma; B-PLL: B-cell prolymphocytic leukemia; ODN-CpG + IL2: oligodeoxynucleotide (DSP30) + interleukin 2; M, million.

[a] In highly proliferative lymphomas, a lower concentration frequently still results in an informative karyotype.

[b] In case of limited material, the choice of the culture depends on the patient age: a unique short culture without mitogens is appropriate in children and adults under 50 years of age.

[c] The duration of culture can be adapted: 48h to 96h

CMAs represent a technical alternative but its inability to detect balanced rearrangements is a major limiting factor, especially for NHL. The other disadvantage is its low sensitivity estimated at 20%. CMAs are applicable to a few indications such as HGBL-11q or PMBL (Table 2).

Optical genome mapping (OGM) is an innovative technology intended to highlight CAs at the level of the whole genome. This nanotechnology is based on optical analysis of labelled DNA fragments to fully characterize the tumour genome at a high resolution with a good sensitivity (see joint article). To date, very few cases of lymphoma have been analyzed by OGM and compared to classical cytogenetic tests [109,110]. Of note, one of main drawbacks of OGM is the use of ultra-high weight DNA fragments, which precludes its use on FFPE samples. OGM is theoretically capable of detecting all types of rearrangement, including complex or cryptic ones. Given the growing number of driver CAs in NHL, the frequency of cryptic or complex rearrangements and evidence of clinical relevance of GC in some entities, OGM, as a 'next generation cytogenomic' technology, could complete - or even replace – the standard cytogenetic analyses in NHL. However, the feasibility, efficacy and diagnostic performance of OGM in lymphomas remain to be demonstrated.

20. Conclusions

CBA and FISH remain central analyses for both diagnostic work-up and prognostic stratification of mature B-cell lymphomas. Application of targeted gene panel sequencing may provide additional valuable clues for more specific classification in difficult cases. Altogether, integration of cytogenetic and molecular data will soon achieve personalized therapy in mature B-cell NHL.

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C. Lefebvre[a,*], L. Veronese[b], N. Nadal[c], J.-B. Gaillard[d], D. Penther[e], A. Daudignon[f], J. Chauzeix[g], F. Nguyen-Khac[h,i], E. Chapiro[h,i]

[a] *Unité de Génétique des Hémopathies, Service d'Hématologie Biologique, CHU Grenoble Alpes, Grenoble, France*

[b] *Service de Cytogénétique Médicale, CHU Estaing, 1 place Lucie et Raymond Aubrac, 63003 Clermont-Ferrand; EA7453 CHELTER, Université Clermont Auvergne, France*

[c] *Service de génétique chromosomique et moléculaire, CHU Dijon, Dijon, France*

[d] *Unité de Génétique Chromosomique, Service de Génétique moléculaire et cytogénomique, CHU Montpellier, Montpellier, France*

[e] *Laboratoire de Génétique Oncologique, Centre Henri Becquerel, Rouen, France*

[f] *Laboratoire de Génétique Médicale - Hôpital Jeanne de Flandre - CHRU de Lille, France*

[g] *Service d'Hématologie biologique CHU de Limoges – CRIBL, UMR CNRS 7276/INSERM 1262, Limoges, France*

[h] *Centre de Recherche des Cordeliers, Sorbonne Université, Université Paris Cité, Inserm UMRS_1138, Drug Resistance in Hematological Malignancies Team, F-75006 Paris, France*

[i] *Sorbonne Université, Groupe Hospitalier Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Service d'Hématologie Biologique, F-75013 Paris, France*

[*] Corresponding author at: Génétique des Hémopathies, Hématologie Biologique, Institut de Biologie et Pathologie, 1er étage, CHU Grenoble Alpes, 38043 Grenoble cedex 9.
E-mail address: clefebvre@chu-grenoble.fr (C. Lefebvre).