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Cytogenetics in the management of myeloproliferative neoplasms, mastocytosis and myelodysplastic/myeloproliferative neoplasms: Guidelines from the Group Francophone de Cytogénétique Hématologique (GFCH)

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ABSTRACT

Myeloproliferative neoplasms, mastocytosis, myeloid/lymphoid neoplasms with hypereosinophilia and tyrosine kinase gene fusions, and myelodysplastic/myeloproliferative neoplasms are clonal hematopoietic cancers that, with the exception of certain entities, have an indolent course.

In addition to their increasingly important role in the diagnosis of these entities, as shown by the recent classification of hematolymphoid tumors in the 5th edition of the World Health Organization and the International Consensus Classification of myeloid neoplasms and acute leukemias, identification of the profile of acquired genetic abnormalities is essential for adapting patient management and early detection of patients at high risk of progression.

Alongside molecular abnormalities, cytogenetic abnormalities play an important role in the diagnosis, prognosis and follow-up of these diseases.

Here, we review the recent literature on the impact of chromosomal abnormalities in these different entities and provide updated cytogenetic recommendations and guidelines for their management.

Introduction

Chronic myeloid leukemia (CML) was the first leukemia in which a chromosomal abnormality (CA) was identified. The t(9;22)(q34.1; q11.2) translocation, characterized years later, became a major diagnostic criterion of this disease, making it a distinct entity from other hemopathies. The discovery of the *JAK2* mutation has also changed the diagnosis of classic myeloproliferative neoplasms (MPNs): polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF). Over time, the discovery and characterization of acquired genetic abnormalities has allowed the individualization of new entities, such as tyrosine kinase rearrangements in myeloid and lymphoid neoplasms with hypereosinophilia and tyrosine kinase gene fusions (MLN-TK), or has constituted major diagnostic arguments for mastocytosis or chronic neutrophilic leukemia (CNL). Cytogenetic and later molecular abnormalities are also relevant for evaluating the prognosis of the disease, guiding therapies and monitoring their efficacy. The explosion in new genome sequencing techniques has conferred further advances in the understanding and diagnostic, prognostic and therapeutic characterization of all hemopathies. However, cytogenetic techniques, due to their availability, decades of accumulated experience, and genome-wide aspects, remain essential in their management.

In this review, we discuss the main CAs of MPNs, MLN-TK, mastocytosis and myelodysplastic/myeloproliferative neoplasms (MDS/MPNs) given the recent changes in the WHO classification of myeloid neoplasms (WHO-HAEM5) and the International Consensus Classification of myeloid neoplasms and acute leukemias (ICC) [1,2]. We provide recommendations for cytogenetic analysis and focus on routine management strategies for these diseases based on the collective experience over decades of the Groupe Francophone de Cytogénétique Hématologique (GFCH).

A summary of these recommendations is presented in Tables 1–4.

Myeloproliferative neoplasms

Chronic myeloid leukemia (CML)

Introduction

CML is characterized by the proliferation of hematopoietic progenitors of the granular lineage without maturation blockage. The natural history of CML evolves in 3 phases: chronic phase (CP), accelerated phase (AP) and blast phase (BP). Its incidence is estimated to be between 10 and 15/1000,000/year (0.5 < 18 years old). The median age of onset is 57 years in Western countries [3], and children and adolescents represent only 5 % of cases. CML leukemic hematopoiesis is induced by the ABL constitutively deregulated tyrosine kinase (TK) from a chimeric BCR::ABL1 protein [4,5]. At the molecular level, the identification of the transcript type is also essential for diagnosis and subsequent molecular monitoring of residual disease. The advent of tyrosine kinase inhibitors (TKIs) targeting ABL1 revolutionized the management of this malignancy. Currently, the 10-year overall survival (OS) of CML patients is between 80 and 90 %, close to that of the general population [6–9], and

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Table 1
Patients characteristics and frequency of common CAs.

	Incidence (/1000,000/year)	Median age at diagnosis (y)	+8	+9	del (20q)	del (13q)	−7/del (7q)	+1q	CK	-Y	References
PV	20	70	2–3 %	4–5 %	3–6.5 %	0.5 %	<1 %	5.5 %	1.5 %	4 %	[48,109]
ET	20	50 (frequency peak around 30)	<1 %	<1 %	1 %	<1 %	<1 %		<1 %	-	[57,109]
MPF	4–7	69–76	11 %	10 %	23 %	18 %	7 %	10 %	14 %	-	[59,110]
CNL	unknown	65	-	-	-	-	-	-	-	-	[64,111]
CEL	0,4	57	24 %	–	12 %	12 %	6 %	12 %	18 %	-	[67,69]
JMML	1,3	<3	2 %	-	-	-	25.5 %/4 %	-	-	-	[76]
MPN-NOS	unknown	–	18.5 %	-	-	-	6 %	-	3	-	[81]
Mastocytosis	10	60	1 %	-	-	-	1 %	1 %	9 %	-	[92,93,112]
CMML	6–9	75	7 %	–	<1 %	–	1.5 %	–	3 %	4 %	[96,97]
MDS/MPN with neutrophilia	<1	70–74	17–27 %	4 %	1.5 %	–	8 %	–	3 %	3 %	[81,100,113]
MDS/MPN with SF3B1 mutation and thrombocytosis	unknown	70–75	4 %	–	<1 %	–	<1 %	–	4 %	5 %	[105]

Table 2
ACAs-Ph+ risk stratification in CML.

ACAs-Ph+ risk stratification according to:		Refs.
WHO—HAEM5	HR: i(17q),−7/del(7q),3q26/*MECOM*, ≥2 ACAs-Ph+/CK[a] LR: +8,+Ph,-Y if isolated[b]	[114]
ELN2020[c]	HR: i(17q),−7/del(7q),3q26/*MECOM*, CK, 11q23/*KMT2A*, +8,+19,+Ph[d] LR: others	[114–116]
Hehlmann 2020 [c]	HR: i(17q)/+17, −7/del(7q),3q26/*MECOM*,+8, +Ph, 11q23/*KMT2A*, +19, +21, CK[e] LR: others	[40]

HR: high risk.
LR: low risk.
[a] :worse survival irrelevant to the emergence phase and time.
[b] :no impact on survival if ACAs observed at diagnosis or in CP.
[c] :ACAs observed at any time.
[d] :high risk ACA predict a poorer response to TKIs and a higher risk of progression.
[e] :High-risk ACA at low blast counts identify end-phase CML earlier than current diagnostic systems.

cessation of treatment has become a major goal for most patients.

Chromosomal aberrations

A classical balanced reciprocal translocation t(9;22)(q34.1;q11.2) resulting in the generation of a *BCR::ABL1* fusion on the derivative chromosome 22 is detectable on karyotype in 95 % of cases. In 5 % of cases, the alteration is presented as a variant translocation with 3 or more partners (variant translocation t(9;22;v)) or as an insertion, not detectable on karyotype (masked Ph) but revealed by *fluorescence in situ hybridization* (FISH) with the presence of a *BCR::ABL1* fusion signal at 22q11.2 or more rarely at 9q34 [10]. These variant translocations do not have a negative prognostic impact.

Additional cytogenetic abnormalities (ACAs) in Ph+ cells (ACAs-Ph+) are found in 5–10 % of CMLs diagnosed in CP, 30 % in AP and 80 % in BP [11–15]. The most frequent are +8, +19, duplication of chromosome Ph (+Ph), and i(17q). As a sign of evolution, their emergence at CP is a criterion of high-risk disease according to the European Leukemia Net (ELN) 2020 recommendations [16].

A particular cytogenetic feature in CML is the emergence of ACAs in clones without a Ph chromosome (ACAs-Ph-) whose origin and biological significance are still unknown. ACAs-Ph- are identical to those found in myelodysplastic/myeloproliferative neoplasms, and the most frequent are -Y, +8, del(20q), and −7/del(7q). They may be found at diagnosis of CML or emerge during TKI treatment and persist in patients in CML remission [17–21]. The negative impact of −7/del(7q) ACA-Ph- on event-free survival (EFS) and progression-free survival (PFS) has been recently published [22]. However, ELN2020 no longer distinguishes −7/del(7q) abnormalities as a "warning".

Genetic aberrations

ABL1 mutations. More than 100 resistance mutations are described, T315I the most frequent, emerging during the CML course and upon the TKIs used [23–25]. These should therefore be investigated in cases of resistance to treatment, switching of TKIs or advanced phases of CML.

Other mutations and gene alterations. Mutations outside *ABL1* have been described [26–29]. Some of the most frequent (*ASXL1, IKZF1, RUNX1, BCORL1, GATA2, SETD1B, DNMT3A, TP53*) are associated with recurrent ACAs (*RUNX1* and + 21 [30,31], *TP53* mutations and i(17q) [29,32], *MECOM* alterations and 3q26 rearrangement [28,29,33]).

Prognostic scores and classifications

Four clinically-based prognostic systems can be used at diagnosis (Sokal, Euro, EUTOS and ELTS) [34–37]. In the era of TKIs, the use of the ELTS is the most relevant since this score minimizes the contribution of age at diagnosis and better accounts for mortality related to hematological disease [38].

Several ACAs-Ph+ risk stratification systems have been proposed (Table 2). Wang's team stratified the six most frequent ACAs-Ph+ into 2 prognostic groups based on OS at the time of emergence: the first, consisting of +8, -Y and +Ph, was associated with a rather favorable prognosis (good response to TKIs and better survival), while the second, consisting of i(17)(q10), −7/del(7q) and 3q26 (*MECOM*) rearrangements or with 2 or more abnormalities, was associated with an unfavorable prognosis (poorer response to TKIs and worse survival). From the same cohort, Gong et al. [39] stratified the transformation risk of ACAs-Ph+ at emergence into a high-risk group (HR) with rapid blastic transformation encompassing 3q26 abnormalities, −7/del(7q), and i(17)(q10) alone or within a complex karyotype (CK: ≥ 3 CAs) and 2 intermediate-risk groups with distinct latencies of blastic transformation: int-1 (+8, +Ph, other isolated ACAs) and int-2 (CK without HR). In this study, -Y was not considered, and it was also highlighted that only −7/del(7q) abnormalities are associated with a significantly higher risk of lymphoblastic transformation.

Table 3
Cytogenetic abnormalities in MLN-TK.

TK gene	number of partners described	Most common partner	Incidence	karyotype (main partner)	Clinical features	Prognosis / TKI response	Reference
4q12-*PDGFRA*	> 60	4q12-*FIP1L1* Others : *CDK5RAP2,BCR, ETV6,STRN, KIF5B*	rare	cryptic	Male predominance, increased tryptase and vitamin B12	Very good/ excellent response to imatinib	[117]
5q32-*PDGFRB*	> 30	12p13-*ETV6* *Others* : 17q21-*COL1A1*	unknown	not cryptic	Male predominance	Very good/ excellent response to imatinib	[84]
8p11-*FGFR1*	> 15	13q12-*ZMYM2* 9q33-*CNTRL* 6q27-*FGFR1OP* 22q22-*BCR*	<100 cases reported	not cryptic not cryptic not cryptic not cryptic	Association with T-lymphoblastic lymphoma CMML-like presentation PV-like presentation CML-like with basophilia	Poor / High rate of response of *FGFR* inhibitor	[91]
9p24-*JAK2*	3	8p22-*PCM1* 12p13-*ETV6* 22q11-*BCR*	rare	not cryptic cryptic not cryptic	Male predominance Association with myelofibrosis		[85]
13q12-*FLT3*	9	12p13-*ETV6* 13q12- *ZMYM2* 14q32- *TRIP11* 2p16- *SPTBN1* 3q13- *GOLGB1* 14q32- *CCDC88C* 17q12-*MYO18A* 22q11- BCR 13q22- ?	<10 cases reported	not cryptic	heterogeneous : myeloid sarcoma, chronic eosinophilic leukemia, CMML MDS and lymphoblastic leukemia/lymphoma frequent extramedullary involvement		[87]
9q34-*ABL1*	–	12p13-*ETV6*	<30 cases reported	cryptic	BCP-ALL and MPN but also T-ALL and AML	Good response to TKI	[89]

Last, Hehlmann et al. [40] reported an HR ACAs-Ph+ based on survival from their occurrence comprising + 8, +Ph, i(17q), +17, +19, +21, 3q26 rearrangements, 11q23(*KMT2A*) rearrangements; −7/del (7q), CK. In this study, HR ACAs-Ph+ predicted a high risk of death due to CML transformation even with low blast counts, suggesting HR ACAs-Ph+ as an earlier marker of death related to CML than blast thresholds.

As TKIs have revolutionized the treatment of CML, the WHO-HAEM5 has removed the notion of AP and emphasized the poor prognostic factors associated with a high risk of transformation when identified in CP at diagnosis. The emergence of ACAs-Ph+ under TKI or *ABL1* TK domain mutations is also associated with poor prognosis [1].

The ELN2020 update identifies HR ACAs-Ph+ at diagnosis and during the CML course (+8, +Ph, i(17q), +19, −7/del(7q), 11q23 (*KMT2A*), 3q26 (*MECOM*), CK), associated with poorer response to TKI therapy and higher risk of transformation. For these reasons, ELN2020 recommends treating patients with HR ACAs-Ph+ as high-risk patients [38]. Hehlmann's team also recommends that upon identification of an HR ACAs-Ph+, close monitoring should be initiated, and treatment intensification should be considered [40].

Detection of ACAs-Ph- has no impact on OS or CML progression [17–21]. Only −7/del(7q) has been associated with signs of dysmyelopoiesis and an increased risk of developing *de novo* Ph- acute myeloid leukemia (AML) and myelodysplastic syndrome [41–44]. These data were consolidated in the GFCH and FI-LMC collaborative study [22] showing a decreased rate of deep molecular response, increased signs of dysmyelopoiesis and more somatic MDS-like mutations by NGS in this group of patients. Any of these abnormalities present after 3 months of TKI use is associated with a negative impact on EFS and PFS [22].

Only a few data are available on pediatric patients. Within the limits of a small cohort, the team of Karow et al. [45] reported a low percentage of ACAs-Ph+ at diagnosis (6 %) with no obvious impact on the response to treatment.

Recommendations of the GFCH

BM is the sample of choice for chromosome banding analysis (CBA) at diagnosis and follow-up. Failing that, CBA can be performed on blood but only in cases of sufficient myelemia. It is recommended that the analysis be performed on at least 20 metaphases [46]. Additional FISH analysis should be performed only in the absence of t(9;22) to detect variant translocations or cryptic abnormalities. ACAs-Ph+ or CK must be reported because of the associated increased risk of acute transformation. The ELN2020 eliminates routine cytogenetic follow-up of CML [16], except for children [47]. However, re-evaluation by CBA is desirable when a significant increase in residual disease is evaluated by molecular monitoring or in cases of evidence of myelodysplasia, as it could be indicative of clonal evolution, signs of disease progression (ACAs-Ph+) or emergence of ACAs-Ph-. It is also recommended to follow the ACAs-Ph- kinetics clones by conventional cytogenetics, even in complete cytogenetic remission of CML.

Polycythemia vera (PV)

Introduction

PV is a chronic MPN with clonal hematopoietic disorder and red-cell overproduction [1,2].

The major diagnostic criteria of PV are elevated hemoglobin concentration (>165 g/L in men and >160 g/L in women) and/or hematocrit (>49 % in men, >48 % in women), presence of *JAK2* mutation and hypercellularity with trilineage hyperplasia on BM examination [1]. A t (9;22)(q34.1;q11.2)*/BCR::ABL1* must be excluded.

Chromosomal aberrations

No structural or numerical abnormality is specific to PV.

CAs are present in 33 % of cases and increase with disease progression. In the initial polycythemic phase, 20 % of abnormal karyotypes are

Table 4
Recommendations of the GFCH.

	Diagnosis		Follow-up	Type of sample
Pathology	Karyotype	Comments	Karyotype	
CML	Mandatory[1]	*BCR::ABL1* FISH for cryptic aberrations or variant translocation	If non optimal response or treatment failure[2] If evidence of MDS[2]	Bone marrow[3]
PV	Recommended[2]	*BCR::ABL1* exclusion mandatory (peripheral blood) [4]	Recommended if progression or treatment failure[2]	Bone marrow[3]
ET	Recommended if TN[2]	*BCR::ABL1* exclusion mandatory (peripheral blood) [4]	Recommended if progression[2]	Bone marrow[3]
PMF	Recommended [2]	*BCR::ABL1* exclusion mandatory (peripheral blood) [4]	Recommended if progression[2]	Peripheral blood[3] Bone marrow[3]
CNL	Mandatory[2]	*BCR::ABL1*[4], *FIP1L1::PDGFRA*[4], *other PDGFRA, PDGFRB, FGFR1, JAK2, FLT3, other ABL1* rearrangements[5] exclusion	Recommended if progression[2]	Bone marrow[3]
CEL-NOS	Mandatory[2]	*BCR::ABL1*[4], *FIP1L1::PDGFRA*[4], *other PDGFRA, PDGFRB, FGFR1, JAK2, FLT3, other ABL1* rearrangements[5] exclusion	Recommended if progression[2]	Bone marrow[3]
JMML	Mandatory[2]	*BCR::ABL1*[4] and *KMT2A*[5] rearrangement; FISH in case of karyotype failure: −7/del(7q) and +8	Recommended[2]	Bone marrow[3] Peripheral blood[3]
MPN-NOS	Mandatory[2]	*BCR::ABL1*[4], *FIP1L1::PDGFRA*[4], *other PDGFRA, PDGFRB, FGFR1, JAK2, FLT3, other ABL1* rearrangements[5] exclusion	Recommended if progression[2]	Bone marrow[3]
MLN-TK	Recommended[2]	*BCR::ABL1* exclusion[4] *FIP1L1::PDGFRA*[4], *other PDGFRA, PDGFRB, FGFR1, JAK2, FLT3, other ABL1* rearrangements[5]	Recommended if progression[2]	Bone marrow[3]
Mastocytosis	Recommended in non-indolent SM [2]	*BCR::ABL1*[4], *FIP1L1::PDGFRA*[4], *others PDGFRA, PDGFRB* rearrangements[5] exclusion	Recommended if progression[2]	Bone marrow[3]
CMML	Mandatory[2]	*BCR::ABL1* exclusion[4]	Recommended if progression[2]	Bone marrow[3]
MDS/MPN with neutrophilia	Mandatory[2]	*BCR::ABL1* exclusion[4]	Recommended if progression[2]	Bone marrow[3] Peripheral blood[3]
MDS/MPN with SF3B1 mutation and thrombocytosis	Mandatory[2]	*BCR::ABL1* exclusion[4] Reconsider diagnosis if del(5q) or 3q26 abnormality. *SF3B1* mutation > 80 % patients	Recommended if progression[2]	Bone marrow[3]
MDS/MPN NOS	Mandatory[2]	*BCR::ABL1* exclusion[4] Reconsider diagnosis if del(5q) or 3q26 abnormality.	Recommended if progression[2]	Bone marrow[3] Peripheral blood[3]

TN: Triple Negative.
[1] :deadline for results: 7 calendar days.
[2] :deadline for results: 21 calendar days.
[3] :short culture (24 h) with or without growth factors (GCSF). Ensemencement cell concentration: 1 to 2 M/ml.
[4] :Molecular test recommended, FISH if not available.
[5] :Large molecular screening and/or FISH with breakapart probe.

found, including del(20q), +1q, +9, +8 and CK. In the fibrotic phase, del (20q) and partial trisomy 1q are predominant, with 45 % of abnormal karyotypes including 24 % of CK. In the accelerated or blast phase, 90 % of karyotypes are abnormal, and the cytogenetic profile is quite different, with a predominance of CK (69 %), including −7/del(7q) (42.8 %), −5/del(5q) (40 %) and −17/del(17p)/i(17q) (25.7 %) [48].

Gene mutations

The *JAK2* p.V617F or *JAK2* exon 12 mutation is the recognized driver event in PV, with ~98 % of mutated cases [49].

It represents a major criterion for diagnosing PV according to WHO-HAEM5 [1] or ICC [2].

If *JAK2* mutation is a crucial event for disease initiation, additional mutations seem to be markers of progression and poor prognosis [50]. In particular, *ASXL1, SRSF2, IDH2, and NFE2* are adverse mutations (~15 % of cases) associated with shortened survival [49,51].

Prognostic scores and classifications

OS in PV is adversely affected by abnormal karyotype, and CAs are risk factors for leukemic transformation regardless of the abnormality(s) detected [52,53].

This adverse prognostic impact persists in cases of secondary myelofibrosis [54]. Of note, in the Mayo Clinic cohort for PV mutation-enhanced international prognostic system assessment, an abnormal karyotype was a mutation-independent risk factor for OS [55].

Tang et al. further stratified the prognostic value of CAs and proposed a classification in three risk categories: "low-risk" (normal karyotype, isolated +8 or +9, and other isolated abnormalities); "intermediate-risk" (isolated del(20q) and double abnormalities including partial 1q trisomy); and "high-risk" groups (CK) [48].

Recommendations of the GFCH

According to ELN, CBA is not mandatory for diagnosis but may be performed as a complementary exploration searching for clonal evidence [1,56]. The GFCH states that karyotyping may be performed at the diagnosis of PV, considering the prognostic impact of CAs in this disease [52,53]. Moreover, BM aspiration for CBA can be realized concomitantly with BM biopsy, which is needed for WHO-HAEM5 diagnostic criteria assessment. CBAs should also be repeated in cases of progression or treatment failure.

Essential thrombocythemia (ET)

Introduction

ET is characterized by a persistent elevated platelet count >450 G/l, BM megakaryocytic proliferation, absence of criteria for other MPN and presence of *JAK2* (50 %), *CALR* (25 %) or *MPL* (5 %) mutations [1,2]; however, 15 % of ET cases are triple negative (TN), and in this case, the presence of clonal markers is needed, and diagnosis relies on cytogenetics or NGS.

Disease progression into fibrotic or leukemia transformation is infrequent (<1 % in the first 10 years of disease).

Chromosomal aberrations

CAs at presentation and during follow-up are rare (<10 %) and without any specificities: -Y, del(20q), +8 and +9 are the most frequent abnormalities (Table 1).

Gene mutations

In addition to the major driver events (*JAK2*V617F, *CALR* or *MPL* mutations), NGS may reveal many other mutations: the most frequent are *TET2* (9–11 %), *ASXL1* (7–20 %), *DNMT3A* (7 %), *SF3B1* (5 %), *SRSF2* (2–3 %), *EZH2* (2–4 %), *TP53* (2–4 %), *RUNX1* (1–2 %) and *CBL* (1–2 %) [55].

Prognostic scores and classifications

Because of the infrequent occurrence of abnormal karyotypes, it is difficult to identify a relationship between CAs and disease progression, and current prognostic scores do not include cytogenetics. However, Gangat *et al.* demonstrated an adverse impact of abnormal karyotypes other than -Y on OS [57].

Recommendations of the GFCH

CBA is not necessary for the diagnosis of ET, except in TN forms. It could also be useful in cases of progression of the disease.

Primary myelofibrosis (PMF)/post-PV myelofibrosis (Post-PV MF)/post-ET myelofibrosis (Post-ET MF)

Introduction

PMF is a *BCR::ABL1*-negative MPN characterized by clonal involvement of CD34+ hematopoietic stem cells, responsible for abnormal proliferation of all three hematopoietic lineages, associated with medullary and splenic fibrosis. It may be classified into early/prefibrotic PMF (pre-PMF) and overt/fibrotic stage PMF [2].

Post-PV MF and post-ET MF, along with the risk of leukemic transformation, form part of the natural history of PV and ET and occur in 6–14 % and 4–11 % of patients, respectively, after 15 years of evolution [58]. Although they appear to be similar to PMF, they are in fact different entities with specific diagnostic criteria [2].

Chromosomal aberrations

CBA identifies a CA in 42.6 % of PMF cases, isolated in 68.2 % of cases and as part of a CK in 13.6 % of cases [59]. The anomalies observed are not specific but recurrent. The most common, accounting for 90 % of abnormal karyotypes, are del(20q), del(13q), +8, +9, +1q and −7/del (7q). Rarer recurrent anomalies may be found, including -Y, del(5q), +21, del(11q), i(17q), del(12p) and inv(3q).

CAs are detected in approximately 30 % of post-ET MF and 40–50 % of post-PV MF. Their profile is similar to that of PV and ET [54].

Gene mutations

JAK2 V617F or exon 12, *CALR* and *MPL* W515 mutations are the classic driver mutations observed in 50–60 %, 20–30 % and 5–10 % of PMF cases, respectively. Ten percent of PMF are TN for these mutations, but non-canonical mutations of *JAK2* and *MPL* may be described.

Additional mutations are more frequent in PMF than in PV and ET in up to 80 % of patients and involve epigenetic regulation, RNA splicing or DNA repair [60,61].

Prognostic scores and classifications

PMF. According to DIPSS Plus, an unfavorable karyotype includes CK or one or two CAs, including +8, −7/del(7q), i(17q), −5/del(5q), del(12p), inv(3) or 11q23 rearrangement [62].

Compared to MIPSS70, MIPSS70 Plus v2 has integrated cytogenetic data. CAs are classified as very high risk (VHR) (single or multiple abnormalities −7, inv(3)/3q21, i(17q), del(12p), del(11q)/11q23 abnormalities, sole autosomal trisomies other than +8 or +9), high risk (HR) (all the abnormalities that are not VHR or favorable), and favorable (normal karyotype, isolated del(20q), del(13q), +9, chr1 translocation/duplication, sex chromosome abnormality including -Y).

In GIPSS, a score exclusively based on genetic markers, VHR and HR karyotypes (same as MIPSS70 Plus v2), absence of type 1/like *CALR* mutation, or presence of *ASXL1, SRSF2* or *U2AF1* Q157 mutations are associated with a poor OS. Poorer leukemia-free survival is predicted by VHR and HR karyotypes and *SRFS2* and *ASXL1* mutations [63].

Post-PV MF/post-ET MF. The above scores have not been validated for these entities.

In the MYSEC cohort, Mora et al. showed that only CK was associated with an increased risk of progression to a blast phase of the disease [54].

Recommendations of the GFCH

According to the WHO-HAEM5, CBA is not mandatory for PMF diagnosis, but its evaluation may be performed as a complementary exploration searching for clonal evidence, especially in TN PMF. However, the GFCH states that karyotyping should be performed at the diagnosis of PMF, considering the prognostic impact of CAs in this disease and in several scoring systems now routinely used. In the same way, we recommend CBA for post-PV MF and post-ET MF. BM cytogenetics is most often unsuccessful due to BM fibrosis. In the event of failure or lack of BM samples, it is possible to perform CBA on blood samples because of the high level of circulating CD34+ hematopoietic precursors.

Chronic neutrophilic leukemia (CNL)

Introduction

CNL is a rare MPN with a poor prognosis, as most patients succumb to disease complications or exhibit transformation to AML. Allogeneic stem cell transplantation is currently the only treatment that can lead to a cure.

CNL is characterized by sustained PB neutrophilia, hypercellular BM and hepatosplenomegaly [1]. Other MPNs and MDS/MPNs should be excluded.

Chromosomal aberrations

CAs at diagnosis are infrequent (10 %) and without any specificities: +8, +9, +21, del(7q), del(20q), del(11q), del(12p), −5, −7 or −17 and CK [64].

Gene mutations

CSF3R mutations constitute the driver genetic event of this disease [65], but their absence does not exclude the possibility of CNL. Moreover, they are not a criterion for the differential diagnosis between aCML and CNL. Additional mutations in *CSF3R*-mutated CNL patients are observed at diagnosis or in the course of the disease (*ASXL1, TET2, SRSF2, U2AF1, SETBP1, JAK2*) [66].

Recommendations of the GFCH

At the time of diagnosis, CBA is mandatory to exclude the presence of a t(9;22)(q34.1;q11.2)/*BCR::ABL1* and other recurrent translocations; at the time of transformation, it is useful to highlight clonal evolution.

Chronic eosinophilic leukemia, not otherwise specified (CEL, NOS)

Introduction

CEL according to WHO-HAEM5 or CEL, NOS according to ICC is a rare MPN [67] for which diagnosis is difficult and requires eliminating the different etiologies of secondary eosinophilia as well as other myeloid neoplasms. This entity is characterized by a clonal proliferation of morphologically abnormal eosinophils and eosinophil precursors responsible for blood, BM and tissue hypereosinophilia. The eosinophil

count is greater than 1.5 × 10^9/L, and eosinophils represent more than 10 % of white blood cells (WBCs) sustained for at least 4 weeks. Alongside BM biopsy, cytogenetic or molecular evidence of clonality are essential for diagnosis [1,2]. The median OS is 11.8 years [67]. The disease may evolve with transformation into acute leukemia, or organs failure secondary to their invasion by abnormal eosinophils. The prognosis remains poor [68,69].

Chromosomal aberrations

CAs occurred in 88.2 % of patients. The more frequent abnormalities are +8, CK, del(13q), del(20q), and chromosome 1 abnormalities [69]. There is no specific recurrent CA. However, the translocation t(5;12)(q31;p13) (*ETV6::ACSL6, ETV6::FNIP1* or *IL3::ETV6*), different from the classic translocation t(5;12)(q32;p13)*/ETV6::PDGFRB*, appears to be recurrent in this entity [70]. The pathophysiological mechanism remains unclear but likely involves deregulation of IL-3 expression, a cytokine involved in eosinopoiesis.

Gene mutations

Their detection provides evidence of clonality and helps distinguish CEL, NOS from hypereosinophilic syndrome (HES) [71]. Recurrent mutations are in *ASXL1, TET2, EZH2, SETBP1,* and *STAT5B* [71,72]. However, it is necessary to consider the frequency of clonal hematopoiesis of indeterminate potential and the difficulty of interpreting these variants in this context.

Activating mutations in genes encoding TK are also highlighted in clonal HE. These cases should be reclassified as myeloid neoplasm with eosinophilia and TK gene fusions [73–75].

Prognostic scores and classifications

Few data are available regarding the prognostic impact of genetic abnormalities. An abnormal karyotype seems to be a predictor of inferior survival, particularly CK which is prognostically relevant for leukemia evolution [69].

Recommendations of the GFCH

Karyotyping remains essential for the diagnosis and characterization of this entity. Renewal CBA to reveal an abnormal clone is desirable during follow-up, especially when it is normal at diagnosis.

Juvenile myelomonocytic leukemia (JMML)

Introduction

According to WHO-HAEM5, JMML is a hematopoietic stem cell-derived MPN of early childhood, dependent on constitutive activation of the RAS pathway [1]. It is characterized by proliferation of the granulocytic and monocytic lineages and theoretical absence of myelodysplastic stigmata. The frequent association of JMML with germline pathogenic gene variants is also acknowledged in WHO-HAEM5. However, according to ICC, JMML is a genetic entity of childhood, defined by constitutive activation of the *RAS* signaling pathway, and must no longer be considered an MDS/MPN [2].

Chromosomal aberrations

A majority of patients (65 %) present normal karyotypes. The remaining exhibit −7 (25 %) or other CAs (10 %), mainly del(7q) and +8. Children with −7 do not differ from those with normal karyotypes with respect to their clinical presentation, but they often harbor a lower WBC count. The presence of a CA at diagnosis does not seem to significantly influence survival [76].

Gene mutations

In 90 % of patients with JMML, somatic or germline-initiating mutations in the canonical *RAS-MAPK* pathway genes *PTPN11, NRAS, KRAS, NF1* or *CBL* can be identified [77,78].

Most patients experience an aggressive clinical course, requiring hematopoietic stem cell transplantation. However, some patients with somatic *NRAS* and germline *CBL* mutations may have spontaneous remission (~15 % of cases) [77]. Conversely, the most aggressive cases seem to be linked to somatic mutations of *PTPN11* [79,80].

GFCH recommendations

According to WHO-HAEM5, a diagnosis of JMML requires combined clinical, laboratory, and molecular criteria. This involves the exclusion of *KMT2A* rearrangements to avoid missing pediatric *KMT2A*-rearranged acute leukemia, which may be indistinguishable from JMML, and which depends on both CBA and FISH analysis using a break-apart probe to explore all possible translocations. Considering its lack of specificity, the presence of a −7 cannot be considered a diagnostic criterion, but it remains a strong argument in the diagnosis-making process. Therefore, CBA is mandatory to eliminate differential diagnosis and to underlie positive diagnosis. It can be performed on BM or PB samples.

In the case of karyotype failure, FISH analysis for −7/del(7q) is desirable; +8 can also be searched for, particularly in cases without −7/del(7q). Finally, molecular tests are essential: the ICC highlights that the presence of molecular alterations in the RAS pathway is mandatory for diagnosis, now that JMML is considered a unique clonal disorder [2].

Myeloproliferative neoplasm, not otherwise specified (MPN-NOS)/MPN, unclassifiable (MPN-U)

Introduction

Previously described as “unclassifiable” (MPN-U), the MPN-NOS entity encompasses patients who do not meet the criteria for other clear-cut MPNs.

Chromosomal aberrations

MPN-NOS is not characterized by a particular cytogenetic profile. Nonspecific CAs have been reported, such as -Y, +8, −7/del(7q) and even CK in rare cases [81].

Recommendations of the GFCH

Considering the exclusionary nature of this entity, CBA is mandatory for diagnosis, especially in triple-negative (*JAK2, CALR* and *MPL*) patients. A large panel of FISH probes may also be useful to eliminate cryptic rearrangements of importance, particularly involving tyrosine kinase gene (see below).

Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions

The entity “Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA, PDGFRB* or *FGFR1*, or with *PCM1-JAK2*”, described in WHO-2017 [82], is now “Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions” (MLN-TK) in WHO-HAEM5 [1]. This change allows the inclusion of all rearrangements involving *JAK2* and those involving *FLT3* and *ETV6::ABL1* fusions in this entity. Eosinophilia, which is in the title, is characteristic but not mandatory. The histological presentation of these disorders may include MDS and MPN/MDS but also AML, mixed phenotype acute leukemia or B- or T-lymphoblastic leukemia/lymphoma.

Clinical and demographic features are summarized in Table 3.

MLN-TK with 4q12/PDGFRA rearrangement

There are more than 60 described partners of the *PDGFRA* gene. The most common partner of *PDGFRA* is *FIP1L1*. The *FIP1L1::PDGRA* fusion, resulting from an 800 kb interstitial deletion of the *CHIC2* gene, located on the 4q12 region, is cryptic on karyotype. The use of a FISH probe localized to the 4q12 region or a generic quantitative reverse transcriptase PCR (qRT−PCR) to detect overexpression of the 3′-regions of

PDGFRA as an indicator of an underlying fusion is mandatory when this disorder is highly suspected [83].

MLN-TK with 5q32/PDGFRB rearrangement

The most common partner of *PDGFRB* is *ETV6* by translocation t (5;12)(q32;p13.2), but more than 30 partners have been described.

Most of these rearrangements are found by karyotype analysis, but FISH or qRT−PCR is necessary to prove involvement of the PDGFRB gene, as several genes encoding eosinophilopoietic cytokines (e.g., IL-3, IL-5, GM-CSF) are localized in the 5q31∼33 region. This confirmation is important to initiate and monitor TKI treatment [84].

MLN-TK with 8p11/FGFR1 rearrangement

This entity comprises all translocations involving the 8p11 band, inducing constitutive activation of the TK receptor *FGFR1* [81].

Only fewer than 100 cases have been reported worldwide, and 14 fusion genes have been described. Some of the *FGFR1* partners may play a role in the disease phenotype.

This entity rapidly progresses to acute leukemia.

MLN-TK with 9p24/JAK2 rearrangement (JAK2r)

MLN-TK with *JAK2*r is no longer a provisional entity in WHO-HAEM5 (1). *PCM1* is the most common partner of *JAK2,* resulting from t(8;9)(p22;p24) translocation [85].

The 9p24 translocation can be cryptic since it involves only a very small fragment of 9p. In these cases, it is necessary to perform FISH, RT−PCR or RNA sequencing to confirm *JAK2r* [86].

MLN-TK with 13q12/FLT3 rearrangement (FLT3r)

FLT3r are particularly rare. The most common partner is *ETV6/* 12p13, but other partners have been described [2,87].

FLT3r is most often found by karyotype analysis, but only approximately one-third of cases with t(13q12;v) harbor *FLT3r* [87]. There are other genes located on band 13q12, such as *CDX2, CCNA1*, and *ZMYM2*. Therefore, *FLT3r* must be confirmed by FISH, RT−PCR or RNA sequencing. The *FLT3* dual-color break-apart FISH probe can be used to detect most of the rearrangements regardless of the breakpoints.

Disease presentations are quite heterogeneous. *FLT3r* is also characterized by frequent extramedullary involvement [87].

MLN-TK with the cryptic t(9;12)(q34;p13)/ETV6::ABL1 fusion

MLN-TK with *ETV6::ABL1* fusion is very rare (<30 cases reported) and occurs in a range of hematologic malignancies, mainly BCP-ALL and MPN but also T-ALL and AML. t(9;12)(q34;p13) is difficult to detect by karyotyping and may result from a complex rearrangement comprising either a translocation and inversion or an insertion of ETV6 into 9q34 or ABL1 into 12p13. Therefore, the incidence of the ETV6::ABL1 fusion might have been underestimated. An additional ABL1 signal by FISH in the absence of BCR::ABL1 fusion can be a clue to search for other ABL1 fusions, often too small to generate a visible signal split even in cryptic insertions. In this context, the combination of the ETV6 and ABL1 break-apart FISH probes are suitable, possible supplementation with an RT−PCR or RNA-based NGS assay [88,89].

Therapeutics

Patients with MLN-TK with *PDGRA* or PDGFRB rearrangement demonstrate an excellent response to imatinib.

Patients with *FGFR1r, JAK2r, FLT3r* and *ETV6::ABL1* fusion have more variable sensitivity to TKIs (for review, [90]). Patients with MLN-TK with *JAK2*r may benefit from new targeted therapies such as *JAK* family protein inhibitors, including ruxolitinib (*JAK2* inhibitor). Pemigatinib, an *FGFR* inhibitor, has demonstrated clinical efficacy in patients with MLN-TK with *FGFR1r* [91].

Recommendations of the GFCH

The GFCH recommends cytogenetic analysis in cases with eosinophilia not explained by properly investigated secondary causes.

The karyotype may be obtained using BM samples. If CBA is not informative, FISH analysis should be performed first for the *PDGFRA* gene, followed by *PDGRB, FGFR1, JAK2* and *ABL1* (eventually *ETV6*). FISH or RT−PCR is also recommended to confirm the involved partners and for subsequent follow-up.

Mastocytosis

Introduction

Mastocytosis is characterized by clonal expansion and accumulation of abnormal clonal mast cells (MCs) in various organs or tissues, driven by activation of the stem cell factor receptor KIT, mostly due to a *KIT* D816V mutation. WHO-HAEM5 recognizes cutaneous mastocytosis, systemic mastocytosis (SM) and mast cell sarcoma [1].

Mastocytosis diagnosis is based on well-defined major and minor criteria, including the pathognomonic dense infiltrate of MCs detected in BM, elevated serum tryptase level, abnormal MC CD25 expression, and the identification of *KIT* D816V mutation.

Chromosomal aberrations

An abnormal karyotype is observed in 15 % to 22 % of SM cases, especially in cases of SM with an associated hematologic neoplasm. None of them are specific to mastocytosis. CAs are associated with inferior survival in univariate analysis, specifically for aggressive forms, but this has not been confirmed in multivariate analysis. High-risk aberrations have been described (−7, CK) and are associated with secondary AML progression or mast cell leukemia. Conversely, del(5q), +8, del(1q) and del(12p) are favorable aberrations [92,93].

Gene mutations

D816 KIT mutation is present in more than 90 % of patients with SM. Other pathogenic *KIT* variations exist and must be examined in the absence of the D816 mutation. In these cases, the help of a referral center may be necessary. In addition to *KIT* mutations, other somatic mutations may contribute to disease evolution, aggressiveness and prognosis (*ASXL1, RUNX1, NRAS*) [94].

Prognostic scores and classifications

Several prognostic scores integrating molecular abnormalities have been proposed, but none of them include CAs.

Recommendations of the GFCH

Given the prognostic value of high-risk CAs, the increased risk of adverse outcomes, and the need to characterize rare entities, the GFCH recommends cytogenetic testing in nonindolent SM.

Myelodysplastic/myeloproliferative neoplasm

Chronic myelomonocytic leukemia

Introduction

Chronic myelomonocytic leukemia (CMML) is the most frequent myeloproliferative/myelodysplastic overlapping syndrome [95,96].

The disease is characterized by the presence of PB persistent monocytosis and BM dysplasia. Given both WHO-HAEM5 and ICC, the absolute monocytosis cutoff has been lowered to 0.5×10^9/L, with the requirement of the presence of BM dysplasia and acquired clonal cytogenetic or molecular abnormality when the number of monocytes is between 0.5 and 1×10^9/L. Myelodysplastic CMML (MD-CMML) and

myeloproliferative CMML (MP-CMML) are individualized if the WBC count is lower or higher than 13×10^9/L, respectively. OS is poor with a high rate of transformation to AML.

Chromosomal aberrations

CAs occur in 30 % of patients. The most frequent are +8, -Y, −7/del (7q), +21, and CK [97].

Gene mutations

TET2, SRSF2, and *ASXL1* are the most frequently mutated genes. RAS pathway mutations are also frequent and associated with the MP-CMML subtype [96].

Prognostic scores and classifications

There are several prognostic scores, with discrepancies in CAs categorization. For CPSS, +8, −7/del(7q) and CK are high-risk CAs, whereas -Y and a normal karyotype are associated with a low risk (97). According to the Mayo-French cytogenetic risk stratification, CK and monosomal karyotype are associated with a high risk, a normal karyotype, -Y, sole der(3q) with a low risk, and others with an intermediate risk [98]. Tang et al. showed that +8 is associated with an increased risk of transformation to AML, but the OS is not significantly different from a normal karyotype [99].

Recommendations of the GFCH

The GFCH states that CBA is mandatory at the diagnosis of CMML, considering that clonality evidence constitutes diagnostic supporting criteria and to exclude entity-specific recurrent rearrangements such as a t(9;22)(q34.1;q11.2). Cytogenetics is also required in several routinely used prognosis scoring systems. GFCH recommends re-evaluating the karyotype in cases of progression or transformation to AML.

Atypical chronic myeloid leukemia - MDS/MPN with neutrophilia

Introduction

In WHO-HAEM5, atypical chronic myeloid leukemia has been renamed MDS/MPN with neutrophilia to avoid potential confusion with CML and to underline the association of myelodysplastic and myeloproliferative features [1]. However, according to ICC, the denomination of atypical CML is still relevant, with a note that the mention of *BCR::ABL1* negativity is no longer useful [2].

Chromosomal aberrations

The karyotype is abnormal in 30 to 50 % of aCML cases. Trisomy 8, +9, del(20q), −7/del(7q) and i(17q) are the most common CAs. None of these CAs are specific to aCML and are similar to cytogenetic findings of other MDS/MPN, MDS and MPN. Of course, t(9;22)(q34.1;q11.2)/*BCR::ABL1* must be excluded with particular attention to rare or atypical variant fusions.

Gene mutations

The absence of MPN-associated driver mutations (*JAK2, CALR, MPL*) is a requirement for diagnosis.

SETBP1 mutations, often associated with *ASXL1* mutations, support the diagnosis [100]. Some other genes may be altered, such as *SRSF2, TET2, NRAS* and *KRAS* in more than 20 % of cases or *EZH2* and *ETNK1* in less than 10 % of cases [101].

Recommendations of the GFCH

CBA on BM or PB samples, considering the proliferative nature of the disease, is mandatory at diagnosis to formally exclude t(9;22)(q34.1;q11.2)/*BCR::ABL1* and CAs associated with MLN-TK. A *BCR::ABL1* FISH probe is mandatory in absence of RT-PCR exploration.

MDS/MPN with SF3B1 mutation and thrombocytosis (MDS/MPN with ring sideroblasts and thrombocytosis)

Introduction

MDS/MPN with *SF3B1* mutation and thrombocytosis is defined by anemia, BM dysplasia with ring sideroblasts and persistent thrombocytosis. This entity, previously known as MDS/MPN with ring sideroblasts and thrombocytosis, has been renamed in WHO—HAEM5 to highlight the importance of *SF3B1* mutations in the diagnostic criteria [1]. However, the denomination of MDS/MPN with ring sideroblasts and thrombocytosis can still be useful in patients harboring ≥15 % of ring sideroblasts without *SF3B1* mutation.

Chromosomal aberrations

Few data are available. CAs are uncommon, and none are recurrent, but various MDS- or MPN-associated CAs may be observed, such as -Y, +8, del(13q) or del(20q) [102]. The presence of del(5q) or 3q26 abnormalities should lead to reconsideration of the diagnosis as MDS [2].

Gene mutations

Mutations in *SF3B1* initiate genetic lesions reported in more than 80 % of patients. Comutations of *JAK2* are the most frequently reported genetic alterations (58 % of cases) [103], but various associated mutations have also been described (*TET2, DNMT3A, SETBP1, ASXL1, CBL, FLT3-Tyrosine Kinase Domain, MPL*) [102–104].

Prognostic scores and classifications

Patnaik et al. have demonstrated that an abnormal karyotype is an independent marker of inferior survival; they also have provided a prognostic model that includes an abnormal karyotype, *ASXL1* or *SETBP1* mutations and hemoglobin level [105].

Recommendations of the GFCH

CBA is mandatory at diagnosis, particularly to exclude other entities, such as MDS with isolated del(5q) or MDS-NOS with 3q26 abnormality. Of note, mutation of *SF3B1* can co-occur in 20 % of MDS with isolated del(5q). Cytogenetic data are also needed for prognosis scoring classification.

Myelodysplastic/Myeloproliferative neoplasm, not otherwise specified

Introduction

This entity comprises previously unclassifiable myelodysplastic/myeloproliferative disorders not meeting the criteria for any other MDS/MPN, MDS or MPN. MDS/MPN-NOS diagnostic criteria have been recently delineated in ICC and include evidence of chromosomal or genomic clonality [2].

Of note, ICC also mentions an MPN unclassifiable (MPN-U) entity, distinct from MDS/MPN-NOS, encountering MPN cases without a clear diagnosis of a specific MPN subtype. In that category, the presence of any clonal marker, including cytogenetics, is also of diagnostic importance.

Chromosomal aberrations

In this rare MPN subtype, the frequency of CAs is poorly known. The most frequent aberrations are similar to other MDS or MPN with -Y, −7/del(7q) or i(17q).

Of note, a new provisional subentity, MDS/MPN with i(17q), either isolated or occurring with one additional abnormality (other than −7/del(7q)), has been classified by ICC experts into the larger group of MDS/MPN—NOS to highlight its aggressive course and the need for new targeted therapeutic options [2].

The presence of the del(5q) or 3q26 abnormality should lead to a reconsideration of the diagnosis as MDS.

Gene mutations

To date, no characteristic mutational signature has been revealed [106].

Prognostic scores and classifications

Although MDS/MPN-U does not have a specific prognostic scoring system, it has been shown that MDS prognostication models can be used to evaluate individual patient risk [107,108].

Recommendations of the GFCH

Considering the exclusionary nature of the diagnosis of MDS/MPN—NOS, CBA is mandatory at diagnosis, particularly to exclude other entities, such as MDS with isolated del(5q) or MDS-NOS with 3q26 abnormality, and to provide proof of clonality.

An informative karyotype may be obtained using BM or PB samples.

Conclusion

Cytogenetics remains a cornerstone for the diagnosis and follow-up of myeloproliferative neoplasms, myeloid/lymphoid neoplasms with eosinophilia and TK gene fusions, mastocytosis and myelodysplastic/myeloproliferative neoplasms. For the vast majority of these entities, the GFCH considers cytogenetic study as mandatory or recommended at diagnosis to identify pathognomonic abnormalities that allow a diagnosis to be made or nonspecific abnormalities that provide evidence of clonality or clarify the prognosis. A cytogenetic reassessment during follow-up is indicated if evolution or transformation is suspected, as the acquisition of additional CAs remains an indicator of disease progression.

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