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CYTOGENETICS (T LIEHR, SECTION EDITOR)

Significance of Cytogenetics in Leukemia Diagnostics

Thomas S. K. Wan[1] · Eleanor K. C. Hui[1] · Margaret H. L. Ng[1]

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Abstract

Purpose of Review Despite the rapid development of molecular techniques, cytogenetic analysis is still an indispensable tool in understanding the pathology of leukemia. The significance of cytogenetics in leukemia is reviewed in terms of its classification, diagnosis, prognosis, and risk stratification, which are all important to guide further treatments based on published clinical trials.

Recent Findings According to the 2016 revised World Health Organization (WHO) classification of leukemia, various well-known clinical practice guidelines in the routine diagnostic workup of leukemias and many large worldwide cohort studies in the leukemia patients' risk stratification banding cytogenetic analysis continue to play essential roles in leukemia diagnostics.

Summary The thought that cytogenetics might be replaced by the advanced molecular techniques in today's genomic world as a phase-out method has not been substantiated. In fact, it remains as an integral part of the diagnostic framework in leukemia evaluation. In the future, cytogenetics together with the molecular methods will form a golden partnership in unraveling leukemia pathogenesis and predicting the outcome of leukemia patients.

Keywords Cancer cytogenetics · Leukemia diagnosis · Chromosomal abnormalities · Prognosis · Karyotype

Introduction

Banding cytogenetics continues to be a fundamental component for the diagnosis, classification, and subsequent risk stratification of leukemia nowadays. Karyotyping of blood cancer cells presents a global view of the acquired abnormalities being present in the entire human genome of a single cell. This advantage of a global picture on the developments of abnormal clones or new clones thus provides evidence for clonal evolution, which mirrors disease progression [1]. In addition, the ploidy status of malignant cells has prognostic implications [2, 3], for example, being hypodiploid or hyperdiploid means dramatically different prognoses for clinical outcome in childhood acute lymphoid leukemia (ALL) for the clinical outcome. It is poor in the former but favorable in the latter case. Endoreduplication of the near-haploid leukemic cells as a mechanism for the associated hyperdiploidy has been well illustrated by us in a previous report [3].

Besides well-known cytogenetic abnormalities associated with specific leukemia subtypes, novel translocation partners can also be easily revealed by cytogenetic analyses [4]. Recently, together with next-generation sequencing (NGS) technology, a rare but clinically significant fusion transcript was detected in a complex karyotype, which further expands the spectrum of disease associations [5].

According to the clinical practice guidelines published by the European Society for Medical Oncology (ESMO), National Comprehensive Cancer Network (NCCN), and the College of American Pathologists (CAP)/American Society of Hematology (ASH), banding cytogenetic analysis is mandatory for the initial diagnostic workup of acute myeloid leukemia (AML) and ALL to guide therapy and predict remission rate, relapse risk, and overall survival outcomes [6, 7, 8••, 9, 10]. As included in the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia, cytogenetics is a central component in the categories of AML with recurrent genetic abnormalities [11••].

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✉ Thomas S. K. Wan
thomaswan@cuhk.edu.hk

[1] Blood Cancer Cytogenetics and Genomics Laboratory, Department of Anatomical and Cellular Pathology, Prince of Wales Hospital, The Chinese University of Hong Kong, Ngan Shing Street, Shatin, Hong Kong, China

WHO Classification of Leukemia

WHO classification of leukemia was first published in 2001, revised in 2008 [12], and further updated in 2016 [11••]. Apart from being based on morphological, cytochemical, immunophenotypic, and clinical features, genetic information was utilized to a great extent in categorization as compared to French-American-British (FAB) system. In view of the fact that WHO has categorized different unique AML subtypes according to cytogenetics, a full karyotype is necessary for all suspected AML cases to fulfill WHO classification at presentation.

Here, we list the WHO classifications for myeloid malignancies:

1. WHO category "AML with recurrent genetic abnormalities" comprises nine recurrent chromosomal balanced translocations and inversions [11••]. Of note, acute promyelocytic leukemia (APL) with translocation t(15;17)(q24.1;q21.2) was renamed to APL with *PML-RARA* in 2016 version, in order to emphasize the importance of this chimeric fusion protein, since this translocation maybe cryptic or appears as complex rearrangement [11••].
2. Patients with nine other recurrent balanced translocations, seven unbalanced chromosomal abnormalities, or complex karyotypes with $\geq$ 3 abnormalities without WHO recurring translocation or inversions are adequate to be classified as "AML with myelodysplasia-related changes (AML-MRC)" provided that $\geq$ 20% blasts are detected in the bone marrow (BM) or peripheral blood (PB), and in the absence of prior therapy.
3. Isolated deletion del(5q) with or without one additional cytogenetic abnormality (except for monosomy 7/ deletion del(7q)) can be classified as "Myelodysplastic syndrome (MDS) subtype." This was updated in 2016 based on the finding that there was no unfavorable effect observed in recent data for these kind of aberrations [11••].

For lymphoid malignancies (see for more details below), B cell lymphoblastic leukemia (B-ALL) is also associated with several recurrent cytogenetic abnormalities. Five recurrent translocations, hypodiploidy or hyperdipoidy, constituted the entity: "B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities." Two significant new provisional entities: *BCR-ABL1*-like ALL and ALL with intrachromosomal amplification of chromosome 21 (iAMP21) have been included in 2016 WHO classification due to their adverse prognosis [11••].

Significance of Cytogenetics in AML

AML risk stratification is classified into favorable, intermediate, and unfavorable groups according to the prognosis that is associated with specific cytogenetic aberrations. However, it may have slight variation in risk classification in different reported cohorts, as especially valid for the intermediate group. AML risk stratification systems have been defined by the Southwest Oncology Group and Cooperative Oncology Group (SWOG/ECOG) and Cancer and Leukemia Group B (CALGB) in 2000 and 2002, respectively [13, 14]. The UK Medical Research Council (MRC) established its own risk stratification in 1998 and revised in 2010 based on large series of 5876 young adult AML patients [15]. In 2010, the European LeukemiaNet (ELN) also published its first edition recommendations for diagnosis and management of AML [16], which has been widely adopted within clinical trials. ELN revised its recommendations in 2017 in order to align with the current version of WHO classification, as well as recent advances in the discovery of the genomic landscape of AML [17••].

Cytogenetics Abnormalities with Favorable Risk in AML

Core-binding factor (CBF) AML cases having a shortage of all types of mature blood cells with translocation t(8;21)(q22;q22) and/or inversion inv(16)(p13.1q22)/ translocation t(16;16)(p13.1;q22) are considered as having a good prognosis; this suggestion is quite consistent among all cooperative group and ELN [13–15, 17••]. Of note, translocation t(15;17)(q24.1;q21.2); *PML-RARA*, which identifies APL, is favorable as well due to the available promising targeted therapy. Patients having one of these three recurrent cytogenetic aberrations can be diagnosed to suffer from AML, regardless of their blast count in BM or PB [12].

Translocation t(8;21)(q22;q22)

It was the first cytogenetic abnormality found by Rowley J.D. in 1973 to be characteristic for AML [18]. It is the most common cytogenetic abnormality in childhood AML, as well having a frequency of 5–10% in adult AML cases. The translocation fuses *RUNX1T1* gene on chromosome 8 with *RUNX1* gene on chromosome 21 results in an in-frame chimeric protein. Loss of sex chromosome and deletion del(9q) are frequent in translocation t(8;21)-positive AML [19]. Translocation t(8;21)(q22;q22) is associated with a favorable outcome in adults; still the incidence decreases with age, particularly for those cases with additional cytogenetic aberrations. In a retrospective cohort study of 916 pediatric patients with translocation t(8;21) conducted by Berlin-Frankfurt-Munster (BFM) study group in 2015, additional deletion del(9q) or gain of chromosome 4 may infer a worse outcome [20].

Inversion inv(16)(p13.1q22) or Translocation t(16;16)(p13.1;q22)

Inversion inv(16)(p13.1q22)/ translocation t(16;16)(p13.1;q22) is another typical aberration for CBF-AML which can secure AML diagnoses irrespective of blast count. AML patients with abnormal eosinophils usually carry such kind of aberrations [21]. Both abnormalities fuse the *CBFβ* gene located in 16q22 to the *MYH11* gene located in 16p13, resulting in a chimeric product. However, inversion inv(16) is found more often than translocation t(16;16). The most frequent secondary chromosome aberration in such cases is trisomy 22, and has predicted a remarkably better outcome in a German-Austrian study [22].

Translocation t(15;17)(q24.1;q21.2)

Reciprocal balanced translocation between *PML* gene located in 15q24.1 and *RARA* gene on 17q21.2 leading to the corresponding fusion gene and the diagnostic hallmark of APL is highly specific. As aforementioned, the significance of *PML-RARA* fusion is the resulting protein rather than the translocation per se. The latter maybe cryptic or appears in complex rearrangements. Patients with APL have a favorable long-term prognosis owing to the development of treatment regimens that combine all-trans-retinoic acid (ATRA) and arsenic trioxide (ATO) [23]. Several variant chromosome translocations involving *RARA* but not *PML* have been recognized in APL: translocation t(11;17)(q23;q21); *ZBTB16-RARA*, translocation t(5;17)(q35;q21); *NPM-RARA*, translocation t(3;17)(q26;q21); *FNDC3B-RARA* or *TBLR1-RARA*, etc. [4, 24]. However, in these cases the prognosis may not be as favorable as in patients with 'original *PML-RARA*' fusion.

Cytogenetics Abnormalities with Adverse Risk in AML

AML with adverse outcome mostly harbor inversion inv(3)(q21.3q26.2) or translocation t(3;3)(q21.3;q26.2), monosomy 5 or deletion 5q, translocation t(6;9)(p23;q34.1), monosomy 7 or deletion 7q, translocation t(9;22)(q34.1;q11.2), rearrangements of 11q23.3/*KMT2A* [except for translocation t(9;11)(p21.3;q23.3)], monosomy 17 or deletion 17p, complex, and/or monosomal karyotypes [15, 25].

Inversion inv(3)(q21.3q26.2) or Translocation t(3;3)(q21.3;q26.2)

Inversion inv(3)(q21.3q26.2) or translocation t(3;3)(q21.3;q26.2) is one of the subtypes newly defined in 2016 WHO classification which are based on recurrent genetic abnormalities. Cytogenetic abnormalities of 3q21.3 are now associated with thrombocytosis and increased dysplastic megakaryocytes [26, 27]. This chromosomal translocation or inversion does not involve in the formation of new chimeric fusion genes but reposition a distal *GATA2* enhancer to activate *MECOM* expression and confers *GATA2* functional haploinsufficiency at the same time [28, 29].

Monosomy 5 or Deletion del(5q)

Cytogenetic abnormalities involving chromosome 5, either monosomy 5 or deletion del(5q), are common findings in de novo MDS and AML, as well as therapy-related myeloid neoplasms (t-MNs). This is one of the unbalanced abnormalities in AML-MRC but with adverse outcome [15, 25, 30]. It is also associated with a high incidence of *TP53* mutation especially in therapy-related AML (t-AML) [31]. However, in MDS with isolated deletion del(5q) (5q- syndrome), which is one of the subtypes in MDS according to 2016 WHO classification, this aberration indicates for a good prognosis, see also revised international prognostic scoring system for MDS (IPSS-R) [32].

Translocation t(6;9)(p23;q34.1)

Translocation t(6;9) involves the juxtaposition of the *DEK* gene in 6p23 with *NUP214* gene in 9q34.1 resulting in a chimeric fusion gene that acts as a transcription factor and alters nuclear transport. It is seen in 1% of patients in a cohort of 5876 younger adults with a newly diagnosed AML [15]. It appears mostly as the sole abnormality and with marrow basophilia and dysplasia [33]. A high incidence of *FLT3* internal tandem duplication (ITD) mutations is associated with translocation t(6;9)-AML [34, 35]. The outcome of translocation t(6;9)-AML is generally poor, with small 5-year overall survival rate and increased risk for relapse [15, 25].

Monosomy 7 or Deletion del(7q)

Loss of chromosome 7 or deletion del(7q) are frequently detected in MDS or t-AML following treatment with alkylating agents. Monosomy 7 is found in juvenile myelomonocytic leukemia (JMML), a subtype of myelodysplastic/myeloproliferative neoplasms (MDS/MPN, acc. to WHO classification) and a rare but aggressive myeloproliferative disease of early childhood [11••]. Most cooperative groups and IPSS-R consider monosomy 7 or deletion del(7q) to be a poor prognostic cytogenetic finding in AML and MDS [15, 25, 32], albeit some data demonstrated that isolated deletion del(7q) had a better survival than patients with monosomy 7 [36]. The three common deleted segments of deletion del(7q) are 7q22, 7q32~33, and 7q36 [37].

Translocation t(9;22)(q34;q11.2)

The reciprocal translocation t(9;22) involves the juxtaposition of *ABL1* gene in 9q34 with *BCR* gene in 22q11.2 (fusion gene

BCR-ABL1). The derivative chromosome 22 is known as Philadelphia (Ph) chromosome and is the hallmark aberration of chronic myeloid leukemia (CML), but can also be found in ALL and rarely in AML. AML with *BCR-ABL1* is now included as provisional entity in the 2016 revised WHO classification [11••]. The differentiation between de novo Ph-positive AML and CML in blastic crisis can be challenging [38]. The prognosis of Ph-positive AML is adverse [15, 25], even is tyrosine kinase inhibitors (TKIs) are applied [39, 40].

Rearrangements of 11q23.3/KMT2A [except for Translocation t(9;11)(p21.3;q23.3)]

Most leukemia patients with 11q23/*KMT2A* gene rearrangements (previously called *MLL* gene and renamed in 2016 revised WHO classification) have a very dismal prognosis [11••, 15]. Translocations of *KMT2A* lead to the generation of in-frame fusions with different partner genes. To date, 135 different *KMT2A* rearrangements and 94 translocation partner genes have been identified [41••]. The six most common translocation partner genes are *AF4* [translocation t(4;11)(q21;q23)], *AF9* [translocation t(9;11)(p22;q23)], *ENL* [translocation t(11;19)(q23;p13.3)], *AF10* [translocation t(10;11)(p12;q23)], *ELL* [translocation t(11;19) (q23;p13.1)], and *AF6* [translocation t(6;11)(q27;q23)] [42, 43]. *KMT2A-AF4* [translocation t(4;11)] is primarily associated with infant ALL, whereas *KMT2A-AF9* [translocation t(9;11)] is more often seen in AML. Of note, translocation t(9;11)(p21;q23) is now recognized as a distinct entity in 2016 revised WHO classification, as having intermediate outcome, which has comparable rates of complete remission and 10-year survival as normal karyotype AML [11••, 15].

Monosomy 17 or Deletion del(17p)

A deletion of 17p or monosomy 17 involves loss of the tumor suppressor gene *TP53* in 17p13.1. The latter is associated with adverse outcomes, even after allogeneic hematopoietic stem cell transplantation (ASCT) [44]. (Partial) monosomy 17p is often accompanied by complex or monosomal karyotypes (see below) as well as by other chromosomal aberrations such as monosomy 5/deletion del(5q) or monosomy 7/deletion del(7q) [44–46].

Complex and/or Monosomal Karyotypes

Complex karyotypic abnormalities confer a poor prognosis. However, definition of a complex karyotype (CK) varies among different risk stratification groups, especially in terms of the number of single aberrations. According to the UK MRC recommendation, ≥ 4 unrelated abnormalities lacking the abovementioned adverse and favorable aberrations are designated as CK [15]. However, the 2017 ELN recommendations classified CK as ≥ 3 unrelated abnormalities as defined before [17••]. In 2008, Breems et al. [47] defined a karyotype with at least two autosomal monosomies or a single autosomal monosomy in the presence of one or more structural cytogenetic abnormalities as monosomal karyotype (MK). AML patients with MK have a particularly poor outcome with a low complete remission and a high relapse rate, and MK has been proposed as a better predictor of unfavorable risk than a CK [48, 49].

Apart from CK and MK, which are well-defined poor prognostic risk factors in AML, several other adverse prognostic indicators have been identified. In a large cohort study of 3526 AML patients by Stolzel et al. in 2016 [50•], patients with a sole hyperdiploid karyotype (a range of 49–80 chromosomes) and without monosomies or structural aberrations have a very poor outcome, irrespective of the number of chromosomal gains. According to Bochtler et al. (2013) [51], clonal heterogeneity at cytogenetic level is an independent adverse prognostic indicator in AML. Interestingly, a recent study of 395 de novo or secondary AML patients reported by Fontana et al. (2018) [52], chromothripsis-positive patients showed a poor overall survival. Chromothripsis is a single event genomic catastrophe that creates chromosomal fragmentation, which may be visible as double minutes, marker chromosomes, derivative, or ring chromosomes [53•, 54].

Cytogenetics Abnormalities with Intermediate Risk in AML

Intermediate-risk cytogenetic indicators provide a great variation among different classification schemes. Cytogenetic abnormalities not classified as favorable or adverse and translocation t(9;11)(p22;q23) are included as intermediate risk in *ELN* recommendations, whereas only the former is included as intermediate risk in the UK MRC [15, 17••]. Normal karyotype, loss of Y chromosome, trisomy 8, trisomy 11, trisomy 13, and trisomy 21 are frequent cytogenetic abnormalities with intermediate risk in SWOG/ECOG and CALGB [25, 55].

Significance of Cytogenetics in ALL

ALL is a heterogeneous disease which is more common in children and can be further subtyped by immunophenotyping into pre B-ALL, mature B-ALL, and T cell acute lymphoblastic leukemia (T-ALL). Current treatment protocols for ALL are found on risk-based therapy in order to have suitable regimens for appropriate risk groups. The development of such risk-based therapy dramatically improved the survival rates of ALL. Prognostic factors of ALL typically include age, white cell count at presentation, immunophenotype, cytogenetics, molecular abnormalities, and response rate to treatment

[56–58]. Cytogenetic investigation plays a vital role both in the classification and prognostication of ALL. In SWOG 9400 study by Pullarkat et al. (2008) [59], cytogenetics turned out to be the most important prognostic factor in adult ALL. Interestingly, there are substantial differences in the frequencies of various recurrent cytogenetic aberrations between childhood ALL and adult ALL [60–62]. Hyperdiploidy and translocation t(12;21)(p13;q22) (*ETV6-RUNX1*), which is cytogenetically cryptic and detectable only by fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR), is more prevalent in childhood ALL. On the contrary, translocation t(9;22)(q34;q11.2) (*BCR-ABL1*) is more common in adult ALL. Furthermore, translocation t(4;11)(q21;q23) (*KMT2A-AF4*), which is found in majority of infant ALL cases, is rare in adult ALL [63].

Pre B-ALL with Low-risk Prognostic Cytogenetic Abnormalities

High Hyperdiploidy

High hyperdiploidy (51–65 chromosomes) is usually associated with clinically favorable outcomes and has a favorable prognosis [60]. It is characterized by a non-random gain of chromosomes, mostly X, 4, 6, 10, 14, 17, 18, and 21 [64]. Patients with trisomies of chromosomes 4, 10, and 17 have been shown to have particularly favorable outcomes, as demonstrated by the analyses from the Pediatric Oncology Group (POG) and Children's Cancer Group (CCG) [65].

Translocation t(12;21)(p13;q22)

In translocation t(12,21) fuses *ETV6* gene in 12p13 with *RUNX1* gene in 21q22. As aforementioned, this translocation is invisible for banding cytogenetic analysis and requires FISH or PCR for accurate detection of the fusion gene. The UK MRC ALL97/99 study demonstrated for childhood B cell ALL patients with translocation t(12;21) a very high event-free survival and high percentage of overall survival rates at 5 years [60].

Pre B-ALL with High-risk Prognostic Cytogenetic Abnormalities

Hypodiplody

Poor outcome in pre B-ALL rises with loss in chromosome numbers in tumor cells. Hypodiploidy can be divided into high hypodiploidy (40–44 chromosomes), low hypodiploidy (32–39 chromosomes), and near haploidy (24–31 chromosomes) [66]. Thus, low-hypodiploid and near-haploid ALL are associated with a very dismal prognosis [67, 68]. Of note, endoreduplication of near-haploid or low-hypodiploid clones is frequent in hypodiploid ALL, which leads to a second hyperdiploid clone [3]. When hyperdiploidy is present as the predominant clone, it may mask the presence of near-haploidy, especially when near-haploid metaphases are ignored owing to poor morphology, or regarded as multiple random chromosome losses. Masked hypodiploidy may be differentiated by observing mainly tetrasomies but not trisomies, which are common in genuine high hyperdiploidy [69]. The distinction of near-haploid ALL and secondary hyperdiploid clones from bona fide hyperdiploid ALL is of great clinical significance, since the prognostic implication is vastly different between the two.

Translocation t(9;22)(q34;q11.2)

Translocation t(9;22)(q34;q11.2) is the most frequent chromosomal abnormality found in adult ALL. The presence of Ph chromosome in ALL is a poor prognosticator, with lower rates of 5-year event-free and an overall survival compared with those without Ph chromosome [61]. Ph-positive ALLs also are associated with additional chromosomal aberrations, typically with additional derivative der(22)t(9;22) or trisomy 21, abnormalities of 9p, trisomy 8, monosomy 7, or trisomy X [70, 71]. The presence of additional chromosomal abnormalities, especially in patients without monosomy 7, appears to have a poor outcome even after ASCT [70, 71]. Although molecular genetic techniques can detect the *BCR-ABL1* gene fusion, cytogenetic analysis is necessary to pick up relevant and novel secondary abnormalities, which may impact on the prognosis.

11q23 /*KMT2A* Translocation

11q23 / *KMT2A* gene rearrangements are common in infant ALL with the most prevalent translocation t(4;11)(q21;q23) (*KMT2A-AF4*) [72]. Infants ALL with translocation t(4;11) experience a very low event-free survival [69].

BCR-ABL1-like (Ph-Like ALL)

Ph-like ALL is a new provisional entity in 2016 revised WHO classification [11••]. It displays a gene expression profile similar to that of Ph-positive ALL but without *BCR-ABL1* gene fusion. It confers a poor prognosis and harbors a wide range of genomic alterations that activate cytokine receptor genes and kinase signaling pathways, making it susceptible to TKI therapy [73]. The frequency of Ph-like ALL exceeds 20% across the adult age ALL spectrum and is independently associated with a poor prognosis [74, 75].

Intrachromosomal Amplification of Chromosome 21 (iAMP21)

iAMP21 is another new provisional entity of the 2016 revised WHO classification and was associated with a high relapse rate when treated with standard therapy [11••]. It can be identified and characterized by FISH method using *ETV6-RUNX1* probe. iAMP21 demonstrates with three or more extra signals of *RUNX1* on a structurally abnormal chromosome 21. Interpretation should be made with caution, as extra *RUNX1* signals can also be due to additional copies of chromosome 21 when using only interphase FISH; however, the latter is characteristic for high-hyperdiploid ALL. As a result of such concerns, the distinctive genomic profile of chromosome 21 is being used to confirm the accuracy of iAMP21 diagnosis [76]. In an international collaborative study of iAMP21, typical secondary chromosome abnormalities were found, including trisomy X, monosomy 7/derivative der(7q), derivative der(11q), and derivative der(12p) [77].

Translocation t(1;19)(q23;p13)

The translocation t(1;19) involves fusion of *TCF3* (19p13) and *PBX1* (1q23) genes. There is another unbalanced form of translocation which has one derivative der(19)t(1;19)(q23;p13), one normal chromosome 19, and two normal chromosomes 1. The prognoses of both forms are similar and have long been associated with a poor outcome [78]. However, recent studies have shown that this adverse outcome can be overcome by a more intensive treatment regimen [79, 80].

Translocation t(17;19)(q22;p13)

Translocation t(17;19) involves *TCF3* gene in 19p13 and *HLF* genes in 17q22. The translocations t(17;19)(q22;p13) and t(1;19)(q23;p13) can be considered as variants of each other. It is an uncommon translocation in B-ALL, having a very dismal prognosis. Most of patients with translocation t(17;19) had relapsed while being under treatment, and eventually died [60, 81]. Owing to the extremely poor outcome of translocation t(17;19), prompt identification of this rearrangement is important, that a more intensive regimen may be applied to such patients.

Dicentric dic(9;20)(p11~13;q11)

The chromosomal abnormality dicentric dic(9;20)(p11~13;q11) is rare, both in pediatric or adult ALL. As this aberration is quite difficult to characterize by banding cytogenetic analysis and often being incorrectly interpreted as monosomy 20 and/or deletion of 9p, FISH remains the most accurate method for its detection. However, as dicentric dic(9;20) has not been shown to result in any gene fusion, no single specific FISH probe can be used to elucidate this aberration. FISH probes consisting of *CDKN2A* at 9p21, centromeric probe of chromosome 9, centromeric probe of chromosome 20, and subtelomeric probe of 20p and 20q may be used instead [82]. Most cases with dicentric dic(9;20) are considered as high-risk group patients, which require a more aggressive treatment, and with increased rates of central nervous system diseases on relapse [83, 84].

Deletion del(9p)

The minimal commonly deleted segment in deletion del(9p) ALL patients is band 9p21, including the tumor suppressor genes *CDKN2A* and *CDKN2B*. The prognostic significance of 9p21 deletion is poor in adult ALL [85]. Nevertheless, conflicting data appeared on the outcome for this abnormality in childhood ALL. Deletion of 9p21 was classified as intermediate-risk group in childhood B-ALL and not associated with adverse prognosis in childhood T-ALL [60, 86].

Mature B-ALL

Translocation t(8;14)(q24;q32) can be recognized in most mature B-ALL cases. This is the same translocation occurring typically in Burkitt's lymphoma, comprising two uncommon variant forms: translocations t(8;22)(q24;q11) and t(2;8)(p12;q24). All these three translocations involve the juxtaposition of the *MYC* gene (8q24) to immunoglobulin heavy-chain locus (14q32), immunoglobulin light-chain lambda locus (22q11), or immunoglobulin light-chain kappa locus (2p12), leading to dysregulation of *MYC* gene expression [87]. Patients with translocation t(8;14) usually have a poor outcome with lower rates of event-free and overall survival [61].

T-ALL

Owing to the low frequency and heterogeneous nature of T-ALL, the prognostic value of cytogenetics is not as well-defined as in B-ALL. In general, T-ALL is an aggressive disease with poor outcome. Although normal karyotype occurs in half of T-ALL, some well characterized and recurrent cytogenetic abnormalities are found to be associated with T-ALL. The aberrations mostly involve T cell receptor genes (*TCR*) on 14q11 (*TCR*-alpha/*TCR*-delta) or *TCR* on 7q34 (*TCR*-beta). Two most common chromosomal rearrangements are translocations t(10;14)(q24;q11) and t(7;10)(q34;q24), both resulting in overexpression of the *TLX1* gene on 10q24; however, the former translocation has a relatively good prognosis. Other translocations include t(1;14)(p32;q11), t(11;14)(p13~15;q11), t(7;9)(q34;q32~34), and t(7;19)(q34;p13) [88]. Notably, two cryptic aberrations are also frequently seen in T-ALL: translocation t(5;14)(q35;q32) juxtaposing *TLX3* gene in 5q35 to

BCL11B gene in 14q32 and deletion of 1p32, which causes a *TAL1-STIL* gene fusion [89].

Significance of Cytogenetics in Chronic Myeloproliferative Neoplasm

According to the 2016 revised WHO classification, MPN can be divided into chronic myeloid leukemia (CML), polycythemia vera (PV), primary myelofibrosis (PMF), essential thrombocythemia (ET), chronic neutrophilic leukemia (CNL), and chronic eosinophilic leukemia (CEL) [11••]. Apart from translocation t(9;22)(q34;q11.2) (*BCR-ABL1*) which is specific in CML, no specific chromosomal abnormalities are clearly defined for the other MPN subtypes. Nowadays, MPN classification or risk stratification is mostly focused on the various well-known driver mutations such as *JAK2*, *CALR*, or *MPL* genes [90]. However, karyotyping still plays a role in confirmation of clonality and clonal evolution follow-up. The most frequent cytogenetic abnormalities harbored in *BCR-ABL*-negative MPNs are deletion of 13q/20q, trisomy 8/9, duplication of 1q, monosomy 7/deletion of 7q, and deletion of 17p /isochromosome of 17q [91, 92].

Significance of Cytogenetics in Chronic Lymphocytic Leukemia

Banding cytogenetic investigation usually fail to delineate the chromosomal abnormalities in chronic lymphocytic leukemia (CLL). This is due to the low mitotic index of the abnormal lymphoid cells in culture, which results in poor growth and/or the result that only normal karyotype cells can be recorded. To date, interphase FISH has been routinely used to identify abnormalities in CLL at presentation. Standard FISH probes used comprise centromeric probe for chromosome 12, deletion probe for *ATM*, *TP53*, and 13q loci; besides, multiplex ligation-dependent probe amplification (MLPA) is routinely used to pick up a larger range of known chromosomal aberrations in CLL. These well-defined genetic markers have prognostic implication to guide the therapy. As FISH method is probe-specific, no other information can be obtained other than these genetic markers. Thus, karyotyping cannot be phased out, which has the benefit for recognition of novel aberrations and the complexity of the abnormal clone. Fortunately, the detection rate of cytogenetic abnormalities can be raised with the utilization of a CpG-oligonucleotide and interleukin 2 [93]. The most common chromosomal abnormality is deletion of 13q14 which has favorable prognosis. Deletion of 11q23 and 17p13 is associated with dismal outcome with the loss of *ATM* gene and *TP53* gene, respectively. Trisomy 12, whether it appears as sole abnormality or not, is considered as an intermediate-risk indicator [94–96].

Conclusions

Nowadays, biology and pathogenesis of hematological malignancies can be delineated rapidly by the advanced high throughput molecular technologies. In contrast, banding cytogenetics through the analysis of chromosomes is more time consuming and labor intensive. Nevertheless, cytogenetics can provide a comprehensive global picture of cancer genome and detect the complexity of the abnormal clone for diagnosis or risk stratification. Thus, a complete karyotype is still one of the criteria in the diagnostic workup of AML or ALL in various clinical practice guidelines. In addition, banding cytogenetics is much cheaper than NGS or other advanced approaches—thus only cytogenetics will be available for the majority of people worldwide, as the new approaches will not be affordable for them. Taken together, the role of cytogenetics is still crucial in leukemia diagnostics in this molecular era with NGS and will probably be used as an essential baseline investigation in the future.

Compliance with Ethical Standards

Conflict of Interest All authors declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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