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Leukemia (PH Wiernik, Section Editor)

Prognostic Significance of Complex Karyotypes in Acute Myeloid Leukemia

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Opinion statement

Acute myeloid leukemia (AML) patients with a complex karyotype (CK-AML) show at least 3 unrelated clonal cytogenetic abnormalities with notoriously poor outcome. Such cases fall into either AML with myelodysplasia-related changes or therapy-related AML in the current World Health Organization classification of AML. Allogeneic stem cell transplantation is one of the only treatment modalities that can provide a long-term survival benefit and is recommended as a consolidative treatment in patients who are able to achieve complete remission. Unfortunately, transplantation is also associated with a higher relapse rate and more than half of CK-AML patients relapse from disease within the first 2 years. The probability of achieving remission with traditional induction using cytarabine and daunorubicin or idarubicin ("7 + 3") is so small that investigational therapies should be considered up front in these patients. Less intensive therapeutic backbones, typically using one of the hypomethylating agents, azacitidine or decitabine, minimize toxicity and show a trend toward the improved overall survival. CPX 351 (Vyxeos) is a liposomal formulation of cytarabine and daunorubicin and this encapsulation leads to prolonged exposure to the two drugs. This drug is approved for AML patients with MDS-related

changes and therapy-related AML, both of which are frequently associated with complex karyotype. Such patients show improved outcome in trials using this combination. Combination therapy that includes venetoclax (BCL2 inhibitor) with hypomethylating agents may also be appropriate for such patients.

Introduction

Acute myeloid leukemia (AML) is a heterogeneous group of diseases resulting from clonal transformation of hematopoietic precursors through the acquisition of chromosomal rearrangements and multiple gene mutations [1]. A significant improvement has occurred over the past 20 years in methods employed to diagnose acute leukemias leading to improvement in diagnosis, classification, and decisions related to the treatment of individual patients [2, 3]. The collective study of AML during the past 30 years has identified specific chromosome aberrations that are frequently found in AML [4•]. Acquired cytogenetic aberrations are detected in 50–75% of the patients with AML [2, 5].

Diagnostic karyotype is the most powerful prognostic factor that predicts for response to induction therapy and survival in patients with AML [6]. Based on cytogenetic findings, patients with AML can be classified into three major cytogenetic risk categories that include favorable, intermediate, and unfavorable. The favorable risk group included patients with t(8;21), t(15;17), inv.(16), or t(16;16). AML patients who are younger than 65 years of age with a favorable karyotype when treated with standard chemotherapy have complete remission rates varying between 85 and 90% range and a 5-year overall survival of 50 to 60%. AML patients with intermediate-risk cytogenetics have significantly worse complete remission rates between 65 and 75%, and a 5-year survival of 35 to 45%. The largest group is the intermediate-risk group that accounts for up to 50% of AML and includes normal karyotype, t(9;11), loss of the Y chromosome, trisomy of chromosome 8, and del(20q). The Medical Research Council (MRC) modified their cytogenetic system of classification in 2010, and the most notable change was moving patients with various translocations involving chromosome 11 from the intermediate-risk group into the unfavorable group [6, 7•].

The unfavorable AML risk group includes complex karyotype, inv.(3) or t(3;3), t(6;9), t(6;11), t(11;19), del(5q), and monosomy of chromosomes 5 or 7 [8, 9]. This group includes AML with complex cytogenetics and monosomal karyotype [4•, 10••, 11]. AML patients with unfavorable-risk cytogenetics have much lower complete remission rates that vary between 45 and 55% and a 5-year survival of only 10 to 20% [12, 13•]. Table 1 demonstrates common recurring cytogenetic aberrations and prognostic risk in AML and the genes involved in these aberrations.

Definition of complex karyotypes

Complex karyotype occurs in 10–14% of all AML patients, and up to 23% among older AML patients [11, 46••]. The definition of complex karyotype (CK) varies based on different classification schemes. It is usually comprised of at least three unrelated chromosomal abnormalities as well as absence of any of the known recurring balanced abnormalities such as t(8;21), inv.(16)/t(16;16), and t(15;17). The Southwest Oncology Group (SWOG) showed that patients with CK but without involvement of either chromosomes 5 or 7 had a complete remission rate of 50% and an overall survival of 20% whereas patients who had

Table 1. Common recurring abnormality and prognostic risks in AML

Cytogenetic abnormality	Genes	Prognosis	Secondary abnormalities	References
inv(16)(p13.1q22)/t(16;16)(p13.1;q22)	*MYH11-CBFB*	Favorable	+ 8, + 22, del(7q), + 2	[13•, 14–16]
t(8;21)(q22;q22.3)	*RUNX1T1*(*ETO*)-*RUNX1* (*AML1*)	Favorable	-X, -Y, del(7q) or – 7, + 8, del(9q)	[14–16]
t(15;17)(q24;q21)	*PML-RARA*	Favorable	+ 8, del(7q), del(9q), ider(17q)	[17]
Normal karyotype	–	Intermediate	–	[13•]
Trisomy 8	*c-MYC* (8q24), *c-MOS* (8q22), *MOZ* (8p11), *ETO* (8q22)	Intermediate	Can be primary or secondary	[18]
Trisomy 6		Intermediate		[19]
-Y	Probably loss of tumor suppressor genes	Intermediate	Age-related, generally considered a secondary event, in association with t(8;21) in AML-M2	[20, 21]
del(12p)	*ETV6*, *CDKN1B*	Intermediate		[16, 22]
-5/5q-, most commonly: del(5)(q13q31), del(5)(q13q33), del(5)(q22q33)	1.5-Mb interval between *D5S413* and *GLRA1* gene deleted, containing around 40 genes	Unfavorable	– 7, + 8, – 20, 20q-, -13/13q, 12p abnormality, often complex, more common in elderly	[15, 23]
-7/7q-	Multiple genes in 7q22-31.1 including *ASNS*, *ACHE*, *EPO*, *PLANH1*, and *MET*	Unfavorable	-5/del(5q), trisomy 8, often complex, more common in elderly	[24–26]
Inv(3)(q21q26)/t(3;3)(q21;q26)	*RPN1-MECOM* (*EVI1*)	Unfavorable	-7/7q-, del(5q), complex karyotype, monosomal karyotype	[15, 16, 27]
11q23 abnormality:				
t(1;11)(q21;q23)	*KMT2A-MLLT11*(*AF1q*)	Excellent		[28]
t(9;11)(p22;q23)	*KMT2A-MLLT3*(*AF9*)	Intermediate	+ 8, + 19	[29]
t(6;11)(q27q23)	*KMT2A-MLLT4*(*AF6*)	Unfavorable	+ 8, + 3, + 19, + 21	[30, 31••]
t(10;11)(p12;q23)	*KMT2A-MLLT10*(*AF10*)	Unfavorable	inv(11)	[31••]
t(11;19)(q23;p13.1)	*KMT2A-ELL*	Unfavorable	+ 8	[31••]
t(11;19)(q23;p13.3)	*KMT2A-MLLT1* (*ENL*)	Unfavorable	+ X, + 6, + 8	[32]
t(11;16)(q23;p13.3)	*KMT2A-CREBBP*	Unfavorable	Therapy-related	[33]
t(2;11)(p21;q23)	*KMT2A*	Unfavorable	Del(5), (q13q33), therapy-related	[34]
17p abnormality (i17q, 17p-, -17)	*TP53*	Unfavorable	Complex karyotype, abnormalities of chromosomes 5 and 7	[35]
20q abnormality:				
Del(20q)		Unfavorable		[36]

Table 1. (Continued)

Cytogenetic abnormality	Genes	Prognosis	Secondary abnormalities	References
	TPO1-OMIN 126420, *PLC1*, *HNF4*, *ADA*, *KRML*		del(5q), trisomy 8, deletions or translocations involving 13q and trisomy	
ider(20q)	Loss of tumor suppressor genes (*L3MBTL*, *ADA*) and gene dosage effect	Unfavorable	21 2 copies of ider(20q), – 7, complex karyotype	[37]
21q abnormality (+ 21, i(21q), psu dic(21q), or r(21))	*RUNX1*, *cystathionine-b-synthetase* (*CBS*; 21q22.3)	Unfavorable	-5/5q- and -7/7q-, + 8	[38]
t(6;9)(p23;q34)	*DEK-NUP214*	Unfavorable	+ 8, + 13, + 21	[39]
t(9;22)(q34;q11)	*ABL1-BCR*	Unfavorable	del(7q)	[40]
t(7;12)(q36;p13)	*MNX1*(*HLXB9*)-*ETV6*	Unfavorable	+ 19,+ 8,+ 13,+ 22	[41]
t(8;16)(p11;p13.3)	*KAT6A-CREBBP*	Unfavorable	+ 8, complex karyotype	[42]
t(1;22)(p13;q13)	*RBM15-MKL1*	Unfavorable	2, + 19, + der(1)t(1;22), + 6,+ 21	[43]
Complex karyotype (≥ 3 abnormalities)	–	Unfavorable	–	[19]
Monosomal karyotype	–	Very poor	–	[44•, 45]

complex cytogenetics and involvement of chromosomes 5 or 7 had significantly lower rates [6]. The MRC-defined CK as having at least 5 unrelated abnormalities based on their findings that each additional abnormality in a karyotype significantly decreased rates of complete remission achievement and increased mortality. AML patients with five or some unrelated abnormalities have a 5-year OS significantly worse than those with three or four abnormalities [47•, 48].

Stolzel et al. (2016) redefined and validated a cutoff for karyotype complexity in AML. The findings of their study revealed that patients with a pure hyperdiploid karyotype (comprising ≥ 47 chromosomes) had an adverse risk regardless of the number of chromosomal gains; patients with t(9;11)(p21.3;q23.3) had an intermediate risk not dependent on the number of additional aberrations. In this study, patients with ⩾ 4 abnormalities had an adverse risk and patients with three aberrations in the absence of abnormalities of strong influence had borderline intermediate/adverse risk with a reduced overall survival when compared with patients with a normal karyotype [47•].

Breems et al. proposed the concept of monosomal karyotype (MK) as being defined by the presence of at least two separate autosomal monosomies or one monosomy plus one or more structural abnormality [44•]. The overall frequency of MK in AML varies from 6 to 10% in prior studies but has been reported up to 20% in AML patients over 60 years of age [49]. Weinberg et al. found that AML with MK accounts for 13% of all AML patients and 22% of all AML patients 60 and over and most of the patients with MK have a CK as defined by having three or more unrelated changes. The most common chromosomes lost in MK include 5 and 7 [45]. Other frequent monosomies include chromosomes 17, 18, 16, 5, and 3 [45].

Chromosomal analysis is subjective and defining independent abnormalities is sometimes difficult [47•]. CK often contain numerous chromosome abnormalities that can only be partially or not at all interpreted using standard cytogenetic techniques. Such abnormalities include unbalanced translocations with chromosomal material of unknown origin, marker, or ring chromosomes, homogeneously staining regions, or double minutes, the latter representing cytogenetic equivalents of high-level DNA amplifications. In general, AML patients with CK are characterized by chromosomal gains and losses, rather than balanced translocations, suggesting distinct mechanisms in leukemogenesis [4•]. Trivedi et al. (2017) combined multiplex FISH with conventional cytogenetic analysis in order to analyze complex chromosomal aberrations and identified several rare, novel, and recurrent aberrations involving chromosomes 1, 5, 17, and 11 [9].

Prognosis of complex karyotypes

AML with unfavorable-risk cytogenetics is clinically challenging with markedly poor outcome [6]. Structural aberrations, such as deletion 5q, deletion 7q, and deletion 17p, or aberrations involving 3q, 11q, and 12p are known to be associated with a poor prognosis in AML and are often seen in a CK [50, 51]. AML patients with CK who have received chemotherapy generally have a highly unfavorable outcome and studies indicate that CK is frequently used as an indicator for experimental treatment approaches. Trivedi et al. (2017) suggested that different genetic mechanisms with varying frequencies could have a role in

the pathogenesis of AML as age increased. It is expected that a better understanding of genomic alterations will help researchers to identify new therapeutic targets and improve the prognosis in patients with CK [9].

MK appears to have a worse prognosis even when compared to those patients with CK. In a study of 733 AML patients with cytogenetic abnormalities, MK was shown to be a stronger prognostic predictor of poor outcome as compared to the traditionally defined CK [44•]. Patients with MK had a 4-year overall survival of 4%, compared with 21% in patients with other unfavorable karyotypes but without MK. Weinberg et al. reported that patients with AML-MK presented at an older age, with lower bone marrow blasts and had morphologic multilineage dysplasia that were predominantly subclassified as having AML with myelodysplasia-related changes (AML-MRC). They concluded that patients with AML-MK had significantly worse OS, DFS, and CR compared with other patients with AML as well as within the AML-MRC group [45]. Other studies have also confirmed that MK is an independent predictor of very poor prognosis in the elderly [49] as well as in a cohort of patients with only unfavorable cytogenetics [52]. The presence of MK in AML patients with CK had an extremely poor prognosis with a 2-year leukemia transformation rate of 29.4% and a median survival of only 6 months [53]. Wierzbowska et al. (2017) analyzed 125 AML patients with CK treated within PALG protocols and found that the overall remission rate of 66 intensively treated patients was 62% in CK^+ MK^- vs. 28% in the CK^+ MK^+ group. In this study, presence of MK and higher karyotype complexity (≥ 5 chromosomal abnormalities) were independent prognostic factors [54]. The relationship between MK and karyotype complexity in AML was also analyzed by Haferlach et al. The authors reported that the difference in survival between CK^+ MK^+ and CK^+ MK^- patients depends on the definition of CK. If CK is defined as ≥ 3 abnormalities, the median time of OS for CK^+ MK^- patients is significantly longer than for CK^+ MK^+ ones. This difference disappears if CK is defined as ≥ 4 abnormalities [55].

AML patients with CK treated with conventional induction and consolidation chemotherapy generally have poor outcome. Among older patients (> 60 years) with 3 or more abnormalities, only 10–40% achieve complete remission and the remission rates are even lower for those with five or more abnormalities. Resistant disease is the main reason for failure to achieve remission and is more common than early death. Even those AML patients with CK who manage to achieve remission tend to relapse in median 6–8 months [4•]. Limited data suggest that prognosis of patients with a CK may also depend on the type of detected abnormalities. Slovak et al. compared the outcome of patients whose CK contained abnormalities of chromosomes 5 and/or 7 (-5/5q- and/or -7/7q-) with that of patients whose CK did not include abnormalities of these chromosomes, and observed that the CR rate was higher in the latter group (50% vs. 37%) as was the probability of surviving 2 years (20% vs. 3%) [13•].

In studies focused exclusively on younger adults AML patients with CK, CR rates were reported to be higher [4•]. The highest remission rates of 75 to 78% have been reported in children, although pediatric AML patients with a CK are limited in number. A CR rate of 67%, which is comparatively a high percentage, was also observed in the MRC study, in which the cytogenetically complex group comprised of young adults ages 14–65. Nonetheless, the long-term

treatment outcome of younger patients with a CK, both for children and adults, is still very unfavorable [56, 57].

TP53 mutations and AML with complex karyotypes

A cytogenetic analysis is a first hierarchical step in the WHO classification of AML [2]. Recently, efforts in classification of AML have focused on identifying molecular markers with prognostic significance. An increasingly exhaustive list of leukemia genes has been gathered from systematic studies of the genomic landscape of AML, such as analyses of data from the Cancer Genome Atlas, and raises a possibility of a fully genomic AML classification scheme. Unfortunately, a high number of genes are mutated in AML and patients typically have more than one driver mutation and multiple competing clones coexisting at any time [58, 59]. Many of the clinical outcome improvements have been made in AML in younger patients, while patients over the age of 60 years at diagnosis have had minimal improvement in the overall dismal survival outcomes [60]. One reason may be the underlying genetic features of AML in older adults: sequencing of the disease of older patients with AML shows an increased frequency of complex mutation patterns and a greater proportion of unfavorable mutations than are seen in younger patients.

There is a strong association between CK and mutation of the *TP53* gene. Several studies have shown *TP53* mutations are frequently detected in patients with AML-CK [61, 62••]. The incidences of *TP53* mutation in AML-CK varied from 53% in a British series, to 60–69% in two German studies. In contrast, *TP53* mutations rarely occurred in patients without CK (2.1%) or 17p chromosomal abnormality (2.8%). Hou et al. found that *TP53* mutation was associated with distinct clinical features and was a poor prognostic factor in AML patients, independent of age, WBC counts, karyotype, and other genetic markers [63]. *TP53*-mutated patients had a higher degree of karyotypic complexity than *TP53* wild-type patients in the subgroup of patients with CK. Furthermore, *TP53* mutations appear to be mutually exclusive of other mutations including *NPM1*, *FLT3*-ITD, and *DNMT3A*. Papaemmanuil found that mutations in *TP53* gene, CK alterations, cytogenetically visible copy-number alterations (aneuploidies), or a combination characterize a distinct group that accounted for 13% of the cohort [62••]. Patients in this subgroup were older and had fewer RAS-pathway mutations than patients in other subgroups and had dismal outcome [62••]. *TP53* status may be assessed using immunohistochemistry. p53 expression may be useful to infer *TP53* mutation status, CK, and/or poor prognosis in situations where other modalities are not readily available [64].

Treatment

Current AML therapy still relies largely on intensive chemotherapy and allogeneic hematopoietic stem cell transplantation (HSCT), at least in younger patients who can tolerate such intensive treatments [65]. This intensive approach has yielded an approximately 60 to 70% chance of the overall survival across different cooperative group protocols [66]. Traditional induction includes 3 days of an anthracycline and 7 days of cytarabine (commonly referred to as "7 + 3" regimens). Post-remission strategies comprise intensive chemotherapy and high-

dose therapy followed by autologous or allogeneic transplantation. Consolidation regimens include single-agent cytarabine at high doses and administration of up to 4 cycles of high-dose cytarabine (2000–3000 mg/m^2, commonly 6 doses per cycle) has been widely used [67]. At the present time, maintenance chemotherapy is not part of standard AML treatment. Initial assessment evaluates whether a patient is considered a candidate for intensive induction chemotherapy and assessment of risk of treatment-related mortality after intensive therapy is usually most relevant in older patients (commonly above the age of 65 years). The prognosis of patients with CK is generally very poor especially for those treated with conventional induction and consolidation [4•].

Allogeneic stem cell transplantation is one of the only treatment modalities that can provide long-term survival benefit for AML patients with CK and is recommended as a consolidative treatment in these patients. Expanded use of mismatched and unrelated donors as well as cord blood means a donor can be found for most patients. Furthermore, non-myeloablative or reduced-intensity conditioning regimens allow allogeneic transplantation in significantly older patients ranging up to 75 years of age. Even so, only a minority of AML patients undergo transplantation because of older age, comorbidities, toxicity of prior therapy, inability to achieve a remission, and early relapse or refractory leukemia [67]. Transplantation in itself is also associated with a higher relapse rate and more than half of CK-AML patients relapse from disease within first 2 years. Presence of abnormalities of chromosomes 5 or 7 is associated with an even higher relapse rate and worse survival benefit [68]. Umukoro (2018) reported that relapse was the main factor responsible for the failure of treatment in patients with AML-CK after transplantation [69]. The authors suggested that conditioning regimens or cellular therapy that can effectively eradicate resistant leukemic clones and prevent post-transplantation relapse are crucially needed as to improve transplantation outcomes in AML-CK patients [69].

Less intensive therapies focus on using one of the hypomethylating agents, specifically azacitidine or decitabine, and therefore minimize the toxicities that are associated with standard "7 + 3" induction. A recent multicenter, randomized trial comparing azacitidine to conventional care regimens, including standard induction chemotherapy, low-dose Ara-c, or supportive care only, suggested a trend toward improved OS for those treated with azacitidine compared to conventional care (10.4 vs. 6.5 months, respectively, $p = 0.1009$) [70]. In a study of decitabine treatment in AML patients, even those with *TP53* mutations had a marked response rate. In this study, during decitabine treatment, *TP53* VAF decreased rapidly to < 5% and was accompanied by marrow blast clearance [71].

Emerging therapies

Venetoclax is an oral inhibitor of the anti-apoptotic protein BCL-2 thought to mediate resistance to typical AML therapy. DiNardo et al. administered venetoclax together with either decitabine or azacytidine to 145 patients considered unfit for standard therapy and with intermediate or adverse cytogenetics and noted a 30-day death rate of 3%, CR rate of 35%, and a CR + CRi rate of 66%. Based on these data, the FDA granted breakthrough therapy designation for venetoclax + either azacytidine or decitabine or with low-dose cytarabine for patients who are ineligible for intensive therapy [72]. CPX 351 is a liposomal formulation of cytarabine

and daunorubicin at a fixed 5:1 M that was determined as optimum in preclinical testing. The liposomal encapsulation leads to prolonged exposure to the two drugs. This drug is approved for AML with myelodysplasia-related changes and therapy-related AML (both of which may have CK) regardless of age even though the trial leading to approval was conducted only in patients aged 60–75 [73]. *FLT3* ITD mutations occur in about 25% of patients aged < 60 years and in about 15% of older patients but most of these cases do not have CK. Midostaurin is an oral multitargeted tyrosine kinase inhibitor active in patients with a *FLT3* mutation and is approved for all AML patients regardless of the age.

Conclusion

This review highlights the use of cytogenetics as a part of the regular diagnostic examination of AML. This information provides a framework for risk stratifying together with an increasing range of molecular markers. This is required for both predicting the risk of relapse in those with normal karyotype and further dissecting out groups of patients with dissimilar prognoses who share particular cytogenetic abnormalities or fall within the same cytogenetic risk group. The integration of pre-treatment parameters remains a central challenge and continues to be so. That integration includes cytogenetics and a number of molecular markers which are expanding exponentially, with an early evaluation of treatment response used to develop robust algorithms that could further refine the risk stratification of AML aimed at guiding consolidation therapy.

Genomic alterations which happen in AML patients with multiple chromosome aberrations are complex; however, recent use of a combination of multicolor FISH, FISH with region-specific probes, comparative genomic hybridization, and molecular genetic techniques has been successful in revealing part of this complexity. It is expected that the biologic basis of leukemic transformation in these patients will be understood better and cytogenetic and molecular subsets of patients with a CK will be identified more easily and efficiently. A patient with AML-CK's response to therapy may vary due to the presence or absence of specific chromosome and/or gene alterations. If such genetic alterations are characterized in more detail that would possibly lead to the development of targeted therapeutic approaches. Such approaches, in turn, could improve the prognosis of AML patients with a CK.

Compliance with Ethical Standards

Conflict of Interest

Yahya Daneshbod, Leila Kohan, and Vahideh Taghadosi declare that they have no conflict of interest. Olga K. Weinberg has received compensation from Jazz Pharmaceuticals for service on an advisory board. Daniel A. Arber has received compensation from Jazz Pharmaceuticals for service on an advisory board and as a consultant.

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.

Publisher's Note

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Rubnitz JE, Gibson B, Smith FO. Acute myeloid leukemia. Pediatr Clin N Am. 2008;55(1):21–51.
2. Haferlach T, Kern W, Schnittger S, Schoch C. Modern diagnostics in acute leukemias. Crit Rev Oncol Hematol. 2005;56(2):223–34.
3. Haferlach T, Schoch C. Moderne Verfahren in der Leukämiediagnostik. Internist. 2002;43(10):1190–202.
4.• Mrózek K. Cytogenetic, molecular genetic, and clinical characteristics of acute myeloid leukemia with a complex karyotype. Semin Oncol. 2008;35(4):365–7.

Overview of complex karyotype definitions and clinical features of AML patients with complex karyotype.

5. Jaffe ES. Pathology and genetics of tumours of haematopoietic and lymphoid tissues. In: Iarc; 2001.
6. Orozco JJ, Appelbaum FR. Unfavorable, complex, and monosomal karyotypes: the most challenging forms of acute myeloid leukemia. Oncology. 2012;26(8):706–12.
7.• Grimwade D, Hills RK, Moorman AV, Walker H, Chatters S, et al. National Cancer Research Institute Adult Leukaemia Working Group. Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. Blood. 2010;116(3):354–6.

Cytogenetic classification in AML based on a large MRC trial.

8. Meng CY, Noor PJ, Ismail A, Ahid MF, Zakaria Z. Cytogenetic profile of de novo acute myeloid leukemia patients in Malaysia. Int J Biomed Sci. 2013;9(1):26.
9. Trivedi PJ, Patel DM, Brahmbhatt MM, Patel PS. Characterization of complex chromosomal rearrangements in acute myeloid leukemia: FISH and multicolor FISH add precision in defining abnormalities associated with poor prognosis. J Blood Res Hematol Dis. 2016;1(2). https://doi.org/10.4172/jbrhd.1000104.
10.•• Mrózek K, Marcucci G, Nicolet D, Maharry KS, Becker H, Whitman SP, et al. Prognostic significance of the European LeukemiaNet standardized system for reporting cytogenetic and molecular alterations in adults with acute myeloid leukemia. J Clin Oncol. 2012;30(36):451.

ELN recommendations for reporting genetic abnormalities in AML.

11. Röllig C, Bornhäuser M, Thiede C, Taube F, Kramer M, Mohr B, et al. Long-term prognosis of acute myeloid leukemia according to the new genetic risk classification of the European LeukemiaNet recommendations: evaluation of the proposed reporting system. J Clin Oncol. 2011;29(20):2758–65.
12. Grimwade D, Walker H, Harrison G, Oliver F, Chatters S, Harrison CJ, et al. The predictive value of hierarchical cytogenetic classification in older adults with acute myeloid leukemia (AML): analysis of 1065 patients entered into the United Kingdom Medical Research Council AML11 trial. Blood. 2001;98(5):1312–20.
13.• Slovak ML, Kopecky KJ, Cassileth PA, Harrington DH, Theil KS, Mohamed A, et al. Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: a Southwest Oncology Group/Eastern Cooperative Oncology Group Study. Blood. 2000;96(13):4075–8.

SWOG trial reported importance of karyotype analysis on outcome of preremission and postremission therapy in AML patients.

14. Appelbaum FR, Kopecky KJ, Tallman MS, Slovak ML, Gundacker HM, Kim HT, et al. The clinical spectrum of adult acute myeloid leukaemia associated with core binding factor translocations. Br J Haematol. 2006;135(2):165–73.
15. Burnett A, Wetzler M, Lowenberg B. Therapeutic advances in acute myeloid leukemia. J Clin Oncol. 2011;29(5):487–94.
16. Bae SY, Kim JS, Ryeu BJ, Lee KN, Lee CK, Kim YK, et al. Acute myeloid leukemia (AML-M2) associated with variant t (8; 21): report of three cases. Cancer Genet Cytogenet. 2010;199(1):31–7.
17. Park J, Jurcic JG, Rosenblat T, Tallman MS. Emerging new approaches for the treatment of acute promyelocytic leukemia. Ther Adv Hematol. 2011;2(5):335–52.
18. Bakshi SR, Brahmbhatt MM, Trivedi PJ, Dalal EN, Patel DM, Purani SS, et al. Trisomy 8 in leukemia: a GCRI experience. Indian J Hum Genet. 2012;18(1):106.
19. Greer JP, Arber DA, Glader B, List AF, Means RT, Paraskevas, et al. Wintrobe's clinical hematology: Thirteen ed. Philadelphia. Lippincott Williams & Wilkins, a Wolters Kluwer business; cytogenetics. 2013; chapter 3: p.52.
20. Wiktor A, Rybicki BA, Piao ZS, Shurafa M, Barthel B, Maeda K, et al. Clinical significance of Y chromosomeloss in hematologic disease. Genes Chromosom Cancer. 2000;27(1):11–6.

21. United KC. Loss of the Y chromosome from normal and neoplastic bone marrows. Genes Chromosom Cancer. 1992;5:83–8.
22. Bilhou-Nabera C. 12p abnormalities in myeloid malignancies. Atlas Genet Cytogenet Oncol Haematol. 1998;2(4):125–6.
23. Hosono N, Makishima H, Mahfouz R, Przychodzen B, Yoshida K, Jerez A, et al. Recurrent genetic defects on chromosome 5q in myeloid neoplasms. Oncotarget. 2017;8(4):6483.
24. Zhang R. Kim Y2, Wang X, Li Y, Lu X, Sternenberger AR, Li S, Lee JY. Genomic copy number variations in the myelodysplastic syndrome and acute myeloid leukemia patients with del(5q) and/or -7/del(7q). Int J Med Sci. 2015;12(9):719–26.
25. Appelbaum FR, Gundacker H, Head DR, Slovak ML, Willman CL, Godwin JE, et al. Age andacute myeloid leukemia. Blood. 2006;107(9):3481–5.
26. Desangles F. 7/del(7q) in adults. Atlas Genet Cytogenet Oncol Haematol. 1999;3(3):139–40.
27. De Braekeleer E, Douet-Guilbert N, Basinko A, Bovo C, Gueganic N, Le Bris MJ, et al. Conventional cytogenetics and breakpoint distribution by fluorescent in situ hybridization in patients with malignant hemopathies associated with inv.(3)(q21;q26) and t(3;3)(q21;q26). Anticancer Res. 2011;31(10):3441–8.
28. Balgobind BV, Raimondi SC, Harbott J, Zimmermann M, Alonzo TA, Auvrignon A, et al. Novel prognostic subgroups in childhood 11q23/MLLrearranged acute myeloid leukemia: results of an international retrospective study. Blood. 2009;114(12):2489–96.
29. Chen Y, Kantarjian H, Pierce S, Faderl S, O'Brien S, Qiao W, et al. Prognostic significance of 11q23 aberrations in adult acute myeloid leukemia and the role of allogeneic stem cell transplantation. Leukemia. 2013;27(4):836.
30. Krauter J, Wagner K, Schafer I, Marschalek R, Meyer C, Heil G, et al. Prognostic factors in adult patients up to 60 years old with acute myeloid leukemia and translocations of chromosome band 11q23: individual patient data-based meta-analysis of the German Acute Myeloid Leukemia Intergroup. J Clin Oncol. 2009;27(18):3000–6.
31.•• Swerdlow S, Campo E, Harris N, Jaffe E, Pileri S, Stein H, et al., editors. World Health Organization classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyons: IARC Press; 2008.

WHO classification of hematologic malignancies.

32. Arsham MS, Barch MJ, Lawce HJ. (Eds.) The AGT Cytogenetics Laboratory Manual, 4th ed. John Wiley & Sons, Hoboken, NJ. 2017.
33. Labis E. t(11;16)(q23;p13.3). Atlas Genet Cytogenet Oncol Haematol. 2009. http://AtlasGeneticsOncology.org/Anomalies/t1116q23p13ID1120.html.
34. Fleischman EW, Reshmi S, Frenkel MA, Konovalova WI, Guleva GP, Kulagina OE, et al. MLL is involved in a t(2;11)(p21;q23) in a patient with acute myeloblastic leukemia. Genes Chromosom Cancer. 1999;24(2):151–5.
35. Shi LH, Ma P, Liu JS, Li Y, Wang YF, Guo MF, et al. Current views of chromosomal abnormalities in pediatric acute myeloid leukemia (AML). Eur Rev Med Pharmacol Sci. 2017;21(4 Suppl):25–30.
36. Bilhou-Nabera C. del(20q) in myeloid malignancies. Atlas Genet Cytogenet Oncol Haematol. 2001;5(1):33–4.
37. Ligon AH, DeAngelo DJ, Atkins L, Dal CP. Isochromosome of a deleted 20q may be a relatively common abnormality in myeloid malignancies. Cancer Genet Cytogenet. 2005;162(1):89–91.
38. Wei CH, Yu IT, Tzeng CH, Fan FS, Hsieh RK, Chiou TJ, et al. Trisomy 21 in acute myeloid leukemia. Cancer Genet Cytogenet. 1996;86(2):177–80.
39. Slovak ML, Gundacker H, Bloomfield CD, Dewald G, Appelbaum FR, Larson RA, et al. A retrospective study of 69 patients with t(6;9)(p23;q34) AML emphasizes the need for a prospective, multicenter initiative for rare 'poor prognosis' myeloid malignancies. Leukemia. 2006;20(7):1295–7.
40. Gajendra S, Sahoo MK. Philadelphia-positive acute myeloblastic leukemia: a rare entity. J Neoplasm. 2016;1:1.
41. Espersen AD, Noren, Nyström U, Abrahamsson J, Ha SY, Pronk CJ, et al. Acute myeloid leukemia (AML) with t (7; 12)(q36; p13) is associated with infancy and trisomy 19: data from Nordic Society for Pediatric Hematology and Oncology (NOPHO-AML) and review of the literature. Genes Chromosom Cancer. 2018;57(7):359–65.
42. Coenen EA, Zwaan CM, Reinhardt D, Harrison CJ, Haas OA, de Haas V, et al. Pediatric acute myeloid leukemia with t (8; 16)(p11; p13): a distinct clinical and biological entity, a collaborative study by the International-Berlin-Frankfurt-Munster AML-study group. Blood. 2013;122:2704–13.
43. Bernstein J, Dastugue N, Haas OA, Harbott J, Heerema NA, Huret JL, et al. Nineteen cases of the t(1;22)(p13;q13) acute megakaryblastic leukaemia of infants/children and a review of 39 cases: report from a t(1;22) study group. Leukemia. 2000;14(1):216–8.
44.• Breems DA, Van Putten WL, De Greef GE, et al. Monosomal karyotype in acute myeloid leukemia. A better indicator of poor prognosis than a complex karyotype. J Clin Oncol. 2008;26:4791–7.

Monosomal karyotype definition and prognostic significance in AML.

45. Weinberg OK, Ohgami RS, Ma L, Seo K, Ren L, Gotlib JR, et al. Acute myeloid leukemia with monosomal karyotype: morphologic, immunophenotypic, and molecular findings. Am J Clin Pathol. 2014;142(2):190–5.
46.•• Dohner H, Estey EH, Amadori S, Appelbaum FR, Buchner T, Burnett AK, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood. 2010;115:453–7.

AML risk classification according to cytogenetic abnormality.

47.• Stölzel F, Mohr B, Kramer M, Oelschlägel U, Bochtler T, Berdel WE, et al. Karyotype complexity and prognosis in acute myeloid leukemia. Blood Cancer J. 2017;6(1):e38.
First clinical study on prognostic significance of karyotype abnormalities in AML.
48. Göhring G, Michalova K, Beverloo HB, Betts D, Harbott J, Haas OA, et al. Complex karyotype newly defined: the strongest prognostic factor in advanced childhood myelodysplastic syndrome. Blood. 2010;116:3766–9.
49. Medeiros BC, Othus M, Fang M, Roulston D, Appelbaum FR. Prognostic impact of monosomal karyotype in young adult and elderly acute myeloid leukemia: the Southwest Oncology Group experience. Blood. 2010;116(13):2224–8.
50. Harrison CJ, Hills RK, Moorman AV, Grimwade DJ, Hann I, Webb DK, et al. Cytogenetics of childhood acute myeloid leukemia: United Kingdom Medical Research Council Treatment trials AML 10 and 12. J Clin Oncol. 2010;28(16):2674–81.
51. Pedersen-Bjergaard J, Andersen MK, Christiansen DH, Nerlov C. Genetic pathways in therapy-related myelodysplasia and acute myeloid leukemia. Blood. 2002;99(6):1909–12.
52. Perrot A, Luquet I, Pigneux A, Mugneret F, Delaunay J, Harousseau JL, et al. Dismal prognostic value of monosomal karyotype in elderly patients with acute myeloid leukemia: a GOELAMS study of 186 patients with unfavorable cytogenetic abnormalities. Blood. 2011;118(3):679–85.
53. Vaidya R, Caramazza D, Begna KH, et al. Monosomal karyotype in primary myelofibrosis is detrimental to both overall and leukemia-free survival. Blood. 2011;117:5612–5.
54. Wierzbowska A, Wawrzyniak E, Siemieniuk-Rys M, Kotkowska A, Pluta A, Golos A, et al. Concomitance of monosomal karyotype with at least 5 chromosomal abnormalities is associated with dismal treatment outcome of AML patients with complex karyotype–retrospective analysis of Polish Adult Leukemia Group (PALG). Leuk Lymphoma. 2017;58(4):889–97.
55. Haferlach C, Alpermann T, Schnittger S, Kern W, Chromik J, Schmid C, et al. Prognostic value of monosomal karyotype in comparison to complex aberrant karyotype in acute myeloid leukemia: a study on 824 cases with aberrant karyotype. Blood. 2012;119(9):2122–5.
56. Grimwade D. Impact of cytogenetics on clinical outcome in AML. In: Karp JE, editor. Acute Myelogenous Leukemia. Totowa, NJ: Humana Press. 2007;p.177–192.
57. Grimwade D, Hills RK. Independent prognostic factors for AML outcome. ASH Education Program Book. 2009;2009(1):385–95.
58. Hernandez JM, Martin G, Gutierrez NC, Cervera J, Ferro MT, Calasanz MJ, et al. Additional cytogenetic changes do not influence the outcome of patients with newly diagnosed acute promyelocytic leukemia treated with an ATRA plus anthracyclin based protocol. A report of the Spanish group PETHEMA. Haematologica. 2001;86(8):807–13.
59. Schlenk RF, Benner A, Krauter J, Buchner T, Sauerland C, Ehninger G, et al. Individual patient data–based meta-analysis of patients aged 16 to 60 years with core binding factor acute myeloid leukemia: a survey of the German Acute Myeloid Leukemia Intergroup. J Clin Oncol. 2004;22(18):3741–50.
60. Chen EC, Fathi AT, Brunner AM. Reformulating acute myeloid leukemia: liposomal cytarabine and daunorubicin (CPX-351) as an emerging therapy for secondary AML. OncoTargets Ther. 2018;11:3425.
61. Ohgami RS, Ma L, Merker JD, Gotlib JR, Schrijver I, Zehnder JL, et al. Next-generation sequencing of acute myeloid leukemia identifies the significance of TP53, U2AF1, ASXL1, and TET2 mutations. Mod Pathol. 2015;28(5):706.
62.•• Papaemmanuil E, Gerstung M, Bullinger L, Gaidzik VI, Paschka P, Roberts ND, et al. Genomic classification and prognosis in acute myeloid leukemia. N Engl J Med. 2016;374(23):2209–2.
A large study on genomic classification and prognosis in AML.
63. Hou HA, Chou WC, Kuo YY, Liu CY, Lin LI, Tseng MH, et al. TP53 mutations in de novo acute myeloid leukemia patients: longitudinal follow-ups show the mutation is stable during disease evolution. Blood Cancer J. 2015;5(7):e331.
64. Fernandez-Pol S, Ma L, Ohgami RS, Arber DA. Immunohistochemistry for p53 is a useful tool to identify cases of acute myeloid leukemia with myelodysplasia-related changes that are TP53 mutated, have complex karyotype, and have poor prognosis. Mod Pathol. 2017;30(3):382.
65. Dombret H, Gardin C. An update of current treatments for adult acute myeloid leukemia. Blood. 2016;127(1):53–61.
66. Creutzig U, Van Den Heuvel-Eibrink MM, Gibson B, Dworzak MN, Adachi S, De Bont E, et al. Diagnosis and management of acute myeloid leukemia in children and adolescents: recommendations from an international expert panel. Blood. 2012;120(16):3187–205.
67. Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424–47.
68. Ciurea SO, Labopin M, Socie G, Volin L, Passweg J, Chevallier P, et al. Relapse and survival after transplantation for complex karyotype acute myeloid leukemia: a report from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation and the University of Texas MD Anderson Cancer Center. Cancer. 2018;124(10):2134–41.
69. Umukoro, C. Post-transplant relapse is a main cause of treatment failure in patients with complex karyotype AML. 2018. Retrieved from https://amlglobalportal.com. Accessed 10 Sept 2018.
70. Dombret H, Seymour JF, Butrym A, Wierzbowska A, Selleslag D, Jang JH, et al. International phase 3 study

of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. Blood 2015;126: 291–299.
71. Welch JS, Petti AA, Miller CA, Fronick CC, O'Laughlin M, Fulton RS, et al. TP53 and decitabine in acute myeloid leukemia and myelodysplastic syndromes. N Engl J Med. 2016;375(21):2023–36.
72. Montalban-Bravo G, Benton CB, Wang SA, Ravandi F, Kadia T, Cortes J, et al. More than 1 TP53 abnormality is a dominant characteristic of pure erythroid leukemia. Blood. 2017;129(18):2584–7.
73. Estey EH. Acute myeloid leukemia: 2019 update on riskstratification and management. Am J Hematol. 2018;93(10):1267–91.