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Acute Myeloid Leukemia with a Complex Karyotype

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Abstract

Patients with acute myeloid leukemia (AML) harboring 3 acquired chromosome aberrations in the absence of prognostically favorable t(8;21)(q22;q22), inv(16)(p13q22)/t(16;16)(p13;q22) and t(15;17)(q22;q21) form a separate category - AML with a complex karyotype. They constitute 10–12% of all AML patents, with the incidence of complex karyotypes increasing with the more advanced age. Recent studies using molecular-cytogenetic techniques (spectral karyotyping, M-FISH) and array comparative genomic hybridization considerably improved characterization of previously unidentified, partially identified or cryptic chromosome aberrations, and allowed precise delineation of genomic imbalances. The emerging nonrandom pattern of abnormalities includes relative paucity, but not absence, of balanced rearrangements (translocations, insertions or inversions), predominance of aberrations leading to loss of chromosome material (monosomies, deletions and unbalanced translocations) that involve, in decreasing order, chromosome arms 5q, 17p, 7q, 18q, 16q, 17q, 12p, 20q, 18p and 3p, and the presence of recurrent, albeit less frequent and often hidden (in marker chromosomes and unbalanced translocations) aberrations leading to overrepresentation of segments from 8q, 11q, 21q, 22q, 1p, 9p, and 13q. Several candidate genes have been identified as targets of genomic losses, e.g., *TP53*, *CTNNA1*, *NF1*, *ETV6* and *TCF4*, and amplifications, e.g., *ERG*, *ETS2*, *APP*, *ETS1*, *FLI1*, *MLL*, *DDX6*, *GAB2*, *MYC*, *TRIB1* and *CDX2*. Treatment outcomes of complex karyotype patients receiving chemotherapy are very poor; they can be improved to some extent by allogeneic stem-cell transplantation in younger patients. It is hoped that better understanding of genomic alterations will result in identification of novel therapeutic targets and improved prognosis in patients with complex karyotypes.

INTRODUCTION

Cytogenetic findings at the time of diagnosis are among the most important independent prognostic factors in patients with acute myeloid leukemia (AML), both adults and children.^{1–14} While t(15;17)(q22;q12-21), t(8;21)(q22;q22) and inv(16)(p13q22)/t(16;16)(p13;q22) are associated with a relatively favorable clinical outcome,^{15–17} several recurrent abnormalities, e.g., inv(3)(q21q26)/t(3;3)(q21;q26) or t(6;9)(p23;q34) bestow very poor prognosis.^{4,6,9} In addition to specific chromosome rearrangements that confer adverse prognosis, a subset of patients whose treatment outcomes have been consistently very poor presents with a complex karyotype defined as the presence of 3 (in some studies 5) chromosome abnormalities.^{2,5–8,11–14} Until recently, this group of patients was not well

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characterized cytogenetically or molecularly because in addition to recognizable chromosome abnormalities, such as deletion of the long arm of chromosome 5, monosomy 7 or trisomy 8, these complex karyotypes contain, sometimes numerous, aberrations that could only be partially or not at all recognized using standard cytogenetic analysis with G- or R-banding.¹⁸ Such aberrations include marker chromosomes, i.e., abnormal chromosomes in which no part can be identified, ring chromosomes of unknown origin, homogeneously staining regions, double minutes and unbalanced translocations, in which the origin of translocated chromosome material cannot be established (usually designated as “add”). The application of molecular-cytogenetic techniques, such as multicolor spectral karyotyping (SKY),^{19–29} multiplex fluorescence *in situ* hybridization (M-FISH)^{28–34} and cross-species color banding,^{35,36} that allow simultaneous display of all human chromosomes in different colors, as well as comparative genomic hybridization (CGH)^{37,38} and array CGH (a-CGH)³⁹ enabled more precise characterization of complex karyotypes. This has also led to identification of several genes whose expression is altered as a result of genomic imbalances in patients in this cytogenetic group.^{40–45} Although these advancements have not yet been translated into improvements of the patients’ outcome, there are promising reports of patients with a complex karyotype responding to treatment that contains inhibitors of histone deacetylase and/or DNA methyltransferase.⁴⁶ This article will briefly review recent advances in delineating cytogenetic, molecular and clinical features of AML patients with a complex karyotype.

DEFINITION AND INCIDENCE

Technically, any karyotype with at least 3 chromosome aberrations, regardless of their type and the individual chromosomes involved, can be referred to as “complex”. Thus, approximately 20% of patients with t(8;21) and around 10% of patients with inv(16)/t(16;16) and of those with t(15;17) would be considered to have a complex karyotype because they harbor 2 secondary aberrations in addition to their respective primary translocation or inversion.^{16,47} However, since several studies have shown that patients with the aforementioned abnormalities constitute separate biological and clinical entities, and that increased karyotype complexity in these cytogenetic groups does not affect adversely clinical outcome in a manner comparable to other patients with 3 (or 5) abnormalities,^{2,6,15,16,47} the category “complex karyotype” excludes patients with t(8;21), inv(16)/t(16;16) and t(15;17). This definition was adopted by studies analyzing the impact of cytogenetics on clinical outcome in AML^{2,5,48} and those focused on improved characterization of genetic rearrangements using multicolor FISH.^{24,34} Some other studies also do not include in the complex karyotype category patients harboring t(9;11) (p22;q23),^{6,12} any balanced rearrangement involving band 11q23,^{11,39} or any “primary balanced abnormality”.³¹

In large series of AML patients, those with a complex karyotype defined as 3 aberrations consistently constituted 10–12% of all patients analyzed,^{3,6,48} whereas patients with 5 aberrations comprised 8–9%.^{2,3,5,6} Moreover, it has become clear that the incidence of complex karyotypes increases with age. Whereas complex karyotypes with 5 aberrations were detected in 6% of AML patients younger than 55 years (including children), they were found in 13% of patients 55 years old and older in the MRC study.⁵ Similarly, in a German series, patients with complex karyotypes with 3 aberrations constituted 8% of patients <60 years of age but 18% of those aged 60 years and above.⁴⁸ Two recent large studies restricted to patients 60 years of age or older¹² and patients older than 60 years¹¹ reported similar percentages of complex karyotypes with 3 abnormalities, 19% and 17%, respectively, although the third study of AML patients aged 60 years reported a lower incidence - 12%.¹⁴ In a population-based study, Schoch et al.⁴³ estimated that the incidence of karyotypically complex AML with 3 aberrations in the German population was 0.05 per

100,000 people aged 21 to 30 years, but it was almost 25 times higher—1.15 per 100,000 people—in the 61 to 70 years age group.

Compared with *de novo* AML, complex karyotypes are approximately twice as common in secondary AML, both therapy-related and evolving from antecedent hematologic malignancy.^{5,43}

MAJOR CYTOGENETIC FEATURES

Even though 3 is the lowest number of chromosome aberrations necessary to consider a karyotype as complex, the vast majority of patients harbor a higher number of aberrations, which in rare cases can reach as many as 30!^{24,30,31} In three large series of AML patients with a complex karyotype analyzed using multicolor FISH, >90 percent of patients had at least 5 abnormalities, with the median number of aberrations being, respectively, 6,³⁰ 8²⁴ and 10.³¹ An example of such a complex karyotype with 8 chromosome abnormalities is depicted in Figure 1.

The modal chromosome number is hypodiploid, i.e., 45 chromosomes, in the majority, between 55% and 75%, of the patients. Approximately one-fourth of patients have a hyperdiploid karyotype, i.e., comprising 47 chromosomes, whereas the karyotype of the remaining patients is pseudodiploid, i.e., the chromosome number is equal to 46 but the karyotype contains clonal chromosome abnormalities.^{24,30,31} This pattern of ploidy is in part a reflection of the fact that whole chromosome losses are more frequent than whole chromosome gains in this group of patients.

Interestingly, whole chromosome losses appear to be more frequent than they really are if only results of standard cytogenetic analysis using G- or R-banding are considered. In such analyses, the most frequently identified as lost are chromosomes no. 7, 18, 20, 21, 5, 12 and 17.²⁴ However, studies using SKY and M-FISH revealed that only a fraction, approximately 30% in one study,²⁴ of chromosomes deemed lost in G-banded karyotypes were confirmed to be truly missing. The remaining chromosomes were not lost entirely but their parts were found in marker and/or ring chromosomes, or in unidentified material attached to a chromosome. Some chromosomes were more likely than others to be structurally rearranged instead of being totally lost. This is particularly true for chromosome 5, true monosomy of which was shown to be very rare, occurring in only about 3% of all patients with a complex karyotype, and also for chromosomes 21, 20 and 12.^{24,30,31,49} On the other hand, monosomy 7 detected in G-banded preparations was confirmed by molecular-cytogenetic techniques in most, and monosomy 18 in one-half of the patients. Importantly, when segments from the apparently missing chromosomes 5, 20, 17, 7, and 18 are found to be hidden in structurally altered chromosomes, the net result of these structural rearrangements is still loss of chromosomal material, mainly from, respectively, chromosome arms 5q, 20q, 17p, 7q, and 18q.²⁴ In contrast, most patients with a supposed monosomy of chromosome 21 harbor cryptic structural rearrangements resulting in overrepresentation of material from the 21q arm, which in some instances amounts to high level amplification.

Consequently, the true pattern of whole chromosome losses in patients with a complex karyotype revealed by SKY and M-FISH analyses includes -7 as the most frequent monosomy, occurring in 20–30% of patients, followed by -18 (20%) and -17 (10–15%).^{24,30,31} With regard to the whole-chromosome gains, which in contrast to chromosome losses can be reliably detected by G-banding alone, trisomy 8 is by far the most frequent - it is present in 10–25% of patients. Other recurrent trisomies observed in 5–10% of patients include +9, +10, +11, +13, +21 and +22.^{24,30,31}

The aforementioned numerical aberrations notwithstanding, the vast majority of aberrations detected in patients with complex karyotypes are structural. Although balanced aberrations such as reciprocal translocations, inversions or insertions can be detected, sometimes only after employing SKY or M-FISH, they are relatively rare.^{24,30,31} Unbalanced abnormalities predominate, and most of them result in net loss of chromosome material. Interestingly, SKY and M-FISH analyses revealed that many abnormalities considered to be described accurately as deletions in G-banded preparations were in fact unbalanced translocations or, less frequently, reciprocal translocations or insertions. In our SKY study of 29 AML patients with a complex karyotype,²⁴ 11 (34%) of 32 deletions in G-banded karyotypes turned out to be such cryptic translocations or insertions, including three of four deletions of chromosome 3, two of three del(7q), and two of 12 deletions of 5q. On the other hand, partial gains of chromosome material caused by structural rearrangements recognized by G-banding are usually confirmed by SKY or M-FISH. These techniques, however, allow uncovering additional cryptic gains of chromosome segments hidden in homogeneously staining regions, double minutes and/or marker and ring chromosomes, with chromosomes 21, 11, 22, 13 and 15 being the most frequently involved.

Table 1 presents the distribution of the most frequent genomic losses and gains (seen in at least 10% of patients) that affect specific chromosome arms as a result of both structural and numerical chromosome abnormalities in AML patients with complex karyotypes. The data come from the three largest studies that used multicolor FISH^{24,30,31} and one large study that used a-CGH.³⁹ Of note, the assay used in the latter study was not capable of detecting imbalances of sex chromosomes X and Y. However, even though aberrations affecting chromosomes X and Y do occur in complex karyotypes,^{24,30,31,50} they are infrequent enough to allow combining results from analyses performed using multicolor FISH with results obtained using a-CGH. The most common by far is loss of material from 5q, seen in 80% of all patients with a complex karyotype. Only 2 other chromosome losses, of 17p and 7q, occur in approximately 50% of cases. Importantly, these abnormalities often occur together, in the same patient, and approximately 85% of all patients harbor loss of at least one of the aforementioned chromosome arms.⁴³ Other imbalances listed in Table 1, both losses and gains, are each seen in less than 30% of the patients.

MOLECULAR GENETIC ALTERATIONS RESULTING FROM CHROMOSOME REARRANGEMENTS

In general, molecular consequences of the majority of segmental losses and gains of specific chromosomes observed recurrently in AML patients with complex karyotypes are not well characterized. However, there has been some progress in identifying genes that likely play a role in leukemogenesis in this subset of AML patients.

The first association between aberrations leading to the loss of chromosome material from 17p and mutations in the *TP53* gene has been reported in the early 1990s,⁵¹ and confirmed by later studies.^{32,52,53} It has been demonstrated that loss of p53 protein function due to *TP53* mutations and/or loss of this gene result in genetic instability and increased cell survival.⁵⁴ Thus, it is likely that *TP53* loss and/or mutations, which occur in most, but not all, patients with a complex karyotype, represent one of the molecular pathways responsible for marked genomic instability, which is manifested by the simultaneous presence of multiple related clones, creation of complex abnormal chromosomes that contain material from 3 or even more separate chromosomes and/or abnormal “sandwich-like” chromosomes that are comprised from several small interchanging segments from two different chromosomes (Figure 2).^{20,24,32}

However, the intensive search for other tumor suppressor genes, especially those located on chromosome arms 7q and 5q, whose one allele would be lost due to a deletion or unbalanced translocation and the other mutated, has been largely unsuccessful. It has been proposed that it is haploinsufficiency, i.e., lower gene expression because of the presence of only one functional allele as a result of deletion of the second allele, affecting many genes mapped to the relatively large segments lost from 5q and 7q, that plays a role in leukemogenesis in patients with a complex karyotype.⁴³ Indeed, two gene-expression studies that compared, respectively, expression of genes located on 5q between complex karyotype patients with loss of 5q material and those with a normal karyotype,⁴³ and expression of genes located on 5q, 7q and 17p between complex karyotype patients with and those without loss of chromosomal material from these chromosome arms,³⁹ revealed that the average expression levels for many genes located in 5q, 7q and 17p were significantly lower in patients harboring rearrangements of these chromosome arms.

The concept of haploinsufficiency does not necessarily exclude, however, the possibility that some of the deleted and/or underexpressed genes are more important than others, and that the elusive 5q- and 7q- tumor suppressor genes may still be identified. A candidate for such a tumor suppressor gene that is mapped to 5q31, the gene encoding α -catenin (*CTNNA1*), has been recently identified.⁵⁵ *CTNNA1* expression was much lower in leukemia-initiating stem cells from AML or MDS patients with del(5q) than in AML or MDS patients without this deletion or in normal hematopoietic stem cells. Importantly, the promoter of the retained *CTNNA1* allele was epigenetically suppressed by methylation and histone deacetylation. When *CTNNA1* expression was restored *in vitro*, cell proliferation was reduced and the cells underwent apoptosis.⁵⁵ This observation is important because it suggests that treatment that includes methyltransferase and histone deacetylase inhibitors capable of re-establishing *CTNNA1* expression might be especially beneficial in patients with complex karyotypes,⁵⁵ 80% of whom harbor loss of 5q material (Table 1).

Another potential target of recurrent genomic loss in complex karyotype AML, identified recently by Rücker et al.,³⁹ is the *NFI* gene, encoding a negative regulator of RAS signaling. *NFI* is located at 17q11, in the smallest region lost in patients with rearrangements of 17q. Interestingly, another study that confirmed the recurrent occurrence of *NFI* deletions in AML patients with a complex karyotype, found *NFI* loss also in patients with inv(16).⁵⁶ Additional candidate genes located within commonly deleted regions in complex karyotype AML are listed in Table 2.

Although in general recurrent gains of chromosome material and high level amplification are less common than segmental losses (Table 1), they too have led to identification of gene alterations that seem to play a role in leukemogenesis of not only cytogenetically complex AML (Table 2), but also other cytogenetic subsets of AML. Following our discovery of a recurrent, mostly cryptic, overrepresentation of 21q material in cytogenetically complex AML patients with an apparent monosomy 21,^{24,57} shown by FISH not to involve amplification of the *RUNX1* gene,²⁴ we applied high-resolution bacterial artificial chromosome-based a-CGH and gene-expression profiling to search for overexpressed genes within the amplified 21q regions.⁴⁰ This study disclosed two regions of 21q amplification: the first containing the most overexpressed gene, *APP*, which encodes a glycoprotein of unknown function previously implicated in Alzheimer's disease, but not in AML, and the second region, in which the most overexpressed were the members of the *ETS* gene family, *ERG* and *ETS2*, encoding transcription factors critical for the control of proliferation, differentiation, and apoptosis.⁴⁰ Importantly, high expression of *ERG* has also been found in a subset of patients with cytogenetically normal AML (CN-AML), and it was demonstrated to confer significantly worse clinical outcome compared with that of CN-AML patients with

low *ERG* expression.^{58,59} The mechanism through which *ERG* is upregulated in CN-AML without 21q amplification is unknown.

The important role of *ETS* gene family overexpression in karyotypically complex AML is underscored by analyses of another recurrently amplified region – 11q23-24. One of the two distinct amplicon clusters identified in this region, located at 11q23.3-q24.1,^{39,41} encompasses the *ETS1* and *FLI1* genes, the latter of which was shown to be significantly up-regulated in cases with increased 11q23 copy numbers.⁴¹ The second amplified region at 11q23.3 contains the *DDX6* and *MLL* genes that were found by Poppe et al.⁴¹ to be the most differentially expressed genes among samples with and without 11q23 copy gain or amplification. Overexpression of *MLL* was associated with increased expression of one of its physiologic downstream targets, *HOXA9*.⁴¹

The third amplicon identified in patients with gains of 11q is located more proximally, at 11q13.5. It was found in one study to coexist with the amplicon containing the *MLL* gene in the same abnormal chromosome 11 in 60% of the patients,⁴⁵ although the frequency of such co-amplification was much smaller in another study.³⁹ The amplicon at 11q13.5 contains the *GAB2* gene, which encodes an adaptor molecule shown to play a role in cytokine receptor signaling in hematopoietic cells.⁴⁵ *GAB2* amplification and overexpression was also found in breast cancer, and it has been suggested that it contributes to mammary carcinogenesis by cooperating with activated *HER2* through activating the SHP2-ERK pathway.⁶⁰ Zatkova et al.⁴⁵ demonstrated using real-time RT-PCR a significant transcriptional up-regulation of *GAB2* in AML patients with concurrent amplification of *MLL*, and proposed that *GAB2* is a novel target of 11q amplification in AML and MDS.

Gains of 8q, detected in 30% of complex karyotype patients, are caused to a large extent by the presence of trisomy 8. Hence, it is not surprising that gene-expression profiling revealed significantly higher average expression levels across many genes located in chromosome 8q.³⁹ However, some complex karyotype cases exhibit high-level amplifications of 8q material, which are often manifested as double minutes containing material from 8q24.^{24,25,39,44} The genomic segment commonly amplified in these double minutes contains five known genes that include *TRIB1* (also known as *C8FW*), *NSMCE2* (*FLJ32440*), and *MYC*.^{39,44} The *MYC* gene was long considered to be main target of 8q24 amplification, and was found overexpressed in a recent study.³⁹ However, Storlazzi et al.⁴⁴ assessed expression of *MYC* by the use of northern blot analysis and, against expectations, did not observe *MYC* overexpression in any of nine cases studied. Instead, the *TRIB1* gene was overexpressed, but only in a subset of cases. Thus, another target or targets of high level amplification of 8q24 in AML with complex karyotype remains to be discovered.

Rücker et al.³⁹ reported rare but recurring high level amplification of 13q12 that encompassed the *FLT3*, *FLT1*, *PAN3*, and *CDX2* genes. The latter gene encodes an upstream regulator of several *HOX* family members whose up-regulation has been associated with leukemogenesis. A recent study from the same group⁶¹ revealed that aberrant expression of *CDX2* is not restricted to cytogenetically complex AML or AML with a rare t(12;13)(p13;q12), in which it was originally discovered,⁶² but could be detected in 90% of 170 AML patients who belonged to several cytogenetic subsets. The highest expression levels of the *CDX2* gene were found in patients with t(9;11)(p22;q23), followed by patients with a normal karyotype, and those with t(15;17), t(8;21), inv(16), a complex karyotype, and other chromosome aberrations.⁶¹ Aside from a few patients with a complex karyotype that contained 13q12 amplification, which correlated well with high *CDX2* expression, the mechanism underlying aberrant expression of *CDX2* in complex karyotype patients without 13q12 amplification or in patients with a non-complex karyotype has not

been established.⁶¹ Likewise, it is currently unknown whether the level of *CDX2* expression has an impact on the AML patients' prognosis.

Recent studies discovered several gene alterations that are relatively frequent in specific cytogenetic groups, and whose presence or absence influences the patients' prognosis.^{63–72} These include internal tandem duplication of the *FLT3* gene (*FLT3*-ITD)^{63–66} and mutations in the *NPM1* gene^{67,68} in patients with CN-AML, and mutations in the *KIT* gene^{69,70} in patients with core-binding factor AML with t(8;21) or inv(16)/t(16;16). Importantly, AML patients with complex karyotypes very rarely harbor *FLT3*-ITD,^{64–66} or mutations in the *NPM1*^{67,68} and *KIT*⁷⁰ genes. Also rare in these patients are mutations in the *NRAS* and *KRAS* genes,⁷³ which were shown to sensitize AML patients to high doses of cytarabine.⁷⁴ Consequently, the impact of the aforementioned mutations on response to treatment and clinical outcome of patients with a complex karyotype appears to be negligible.

CLINICAL OUTCOME

Prognosis of patients with a complex karyotype is in general very poor (Table 3), especially in patients treated with conventional induction and consolidation chemotherapy. Among older adults above the age of 60 years, who constitute the majority of patients with a complex karyotype,⁴³ only 10% to 44% of those who harbor 3 abnormalities achieve a complete remission (CR).^{11,12,14,48} The CR rates for patients with 5 abnormalities are even lower, 7% to 26%.^{5,11,12} Resistant disease is the main reason for failure to achieve a CR, and it is more than twice as common as early death, which nevertheless affects 18% to 28% of elderly patients with a complex karyotype.^{5,11,12,14,48} Almost all patients who achieve a CR relapse. CR durations are short, with medians of 6 to 8 months, and the probabilities or remaining in CR at 3 years are between 0 and 11%, and at 5 years between 0 and 9% (Table 3).

CR rates of karyotypically complex patients are slightly higher in studies restricted to younger adults,^{3,48} and in those that included adults both younger and older than 60 years.^{6,75,76} The highest rates of CR, 75 to 78%, were reported in children, although the outcome data on pediatric AML patients with a complex karyotype are limited.^{8,13} A comparatively high CR rate of 67% was also observed in the MRC study, in which the cytogenetically complex group included 20% of children aged 14 years, and the remaining 80% of adult patients were younger than 56 years.² Nevertheless, the long term treatment outcome of younger patients with a complex karyotype, both children and adults, is still very poor (Table 3).

It has been shown that clinical outcomes of younger patients with a complex karyotype or those classified in an unfavorable cytogenetic prognostic category, which includes complex karyotypes, can be improved by allogeneic hematopoietic stem-cell transplantation (HSCT).^{77,78} Schmid et al.⁷⁷ reported that for complex karyotype patients who underwent allogeneic HSCT following regimen of chemotherapy, reduced-intensity conditioning for HSCT, and prophylactic donor lymphocyte transfusion, the 2-year leukemia-free and overall survival rates were, respectively, 44% and 47%. In another study,⁷⁸ for patients in unfavorable risk group who underwent matched unrelated donor HSCT in first CR, the 5-year disease-free and overall survival rates were, respectively, 27% and 30%, and for patients who were transplanted in second CR, the respective rates were 38% and 36%. However, treatment-related mortality was high.⁷⁸

Interestingly, a recent phase I study evaluating decitabine, a DNA demethylating agent, alone or in combination with valproic acid, a histone deacetylase inhibitor, reported that all four AML patients who achieved a morphologic and cytogenetic CR had a complex karyotype with 5 abnormalities and all were older than 60 years.⁴⁶ Although the CR

durations were relatively short for three of the four patients, this encouraging observation warrants further study with a prospect of developing regimens that would be effective in older adults with a complex karyotype who are not eligible for allogeneic HSCT.

Thus far limited data suggest that prognosis of patients with a complex karyotype may also depend on the kind of detected abnormalities. Slovak et al.³ compared the outcome of patients whose complex karyotype contained abnormalities of chromosomes 5 and/or 7 (-5/5q- and/or -7/7q-) with that of patients whose complex karyotype 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%).³ Likewise, a significantly longer survival of patients with “atypical” complex karyotype compared with survival of patients with “typical” complex karyotype (median, 10.2 vs. 5.4 months) was found in another study.⁴³ In this study,⁴³ a complex karyotype with 3 abnormalities was classified as “typical” if it contained loss of material from at least one of the 3 chromosome arms, 5q, 7q or 17p, as well as at least one additional loss from either 18q21q22, 12p13, or 16q22q24 or gain of a chromosomal segment containing 11q23q25, 1p33p36, 8q22q24, or 21q11q22. Patients with “atypical” complex karyotype constituted a minority of cases, 12–18%, were slightly older and had more often hyperdiploid chromosome number than “typical” cases (54% vs. 19%). In a multivariable analysis, overall survival was associated with age and there was a trend for the association of survival with the type of complex karyotype (“typical” vs. “atypical”). Future studies confirming these results are necessary.

CONCLUSION

Recent studies using multicolor FISH, FISH with region-specific probes, a-CGH and molecular genetic techniques have begun unraveling the complexity of genomic alterations occurring in AML patients with multiple chromosome aberrations. It is hoped that these and future studies will not only lead to better understanding biologic basis of leukemic transformation in these patients but will also result in identification of cytogenetic and molecular subsets of patients with a complex karyotype that may respond differently to therapy because of the presence or absence of specific chromosome and/or gene alterations. Further characterization of such genetic alterations will likely allow development of targeted therapeutic approaches that will improve the currently very poor prognosis of AML patients with a complex karyotype.

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Figure 1.

Complex karyotype containing 8 chromosome abnormalities detected in a patient with acute myeloid leukemia, analyzed using spectral karyotyping (SKY). Each chromosome is represented twice, by G-banding-like inverted and contrast-enhanced DAPI-stained image on the left and SKY image shown in classification colors on the right. This karyotype contains several chromosome abnormalities relatively common in AML with a complex karyotype: an unbalanced translocation between chromosomes 3 and 17 leading to loss of material from 3p and chromosome 17 (yellow arrow), an unbalanced translocation between chromosomes 3 and 5 resulting in partial loss of 5q (green arrow), trisomy of chromosome 8 (blue arrow), loss of one copy of chromosome 17 (grey arrow) and a complex rearrangement between chromosome 10 and 21 leading to gain of material from 21q (red arrow). Also present are: a complex rearrangement of chromosome 15 resulting in amplification of 15q material (white arrow), abnormal chromosome 10 (orange arrow) and a small marker chromosome whose origin could not be established reliably by SKY technique (pink arrow).

Figure 2.

Metaphase cells from an AML patient with a complex karyotype that contains an abnormal “sandwich-like” derivative chromosome comprised from several interchanging segments from chromosomes 7 and 21, analyzed using SKY (A) and whole-chromosome-painting probes for chromosomes 7 (B) and 21 (C). Inverted and contrast-enhanced DAPI images are shown on the left. SKY in display colors (A) and FISH images (B and C) are shown on the right. Long arrows point to the centromeric area of the abnormal “sandwich-like” derivative chromosome, short arrows denote normal chromosomes 7 (A and B) and 21 (A and C). **A:** Full metaphase cell analyzed using SKY. **B.** Partial metaphase hybridized with the whole-chromosome-painting probe for chromosome 7. **C.** Partial metaphase hybridized with the whole-chromosome-painting probe for chromosome 21.

Table 1

Frequencies of the most common genomic imbalances (losses and gains) affecting specific chromosome arms in AML patients with complex karyotypes revealed by studies using multicolor FISH and array CGH techniques

Chromosome arm	Study (no. of patients)				Total (n=250) ^a
	Mrózek et al. ²⁴ (n=29)	Van Limbergen et al. ³⁰ (n=36) ^b	Schoch et al. ³¹ (n=125)	Rücker et al. ³⁹ (n=60)	
Abnormalities resulting in loss of chromosome material					
5q	76%	81%	82%	77%	80%
17p	62%	25%	53%	55%	50%
7q	59%	44%	46%	45%	47%
18q	41%	11%	30%	30%	29%
16q	24%	25%	NR	32%	28%
17q	24%	36%	NR	22%	27%
12p	41%	17%	27%	18%	25%
20q	38%	14%	NR	18%	22%
18p	41%	11%	NR	15%	20%
3p	24%	8%	NR	20%	18%
12q	14%	6%	NR	20%	14%
13q	10%	17%	NR	12%	13%
11q	14%	6%	NR	12%	10%
Abnormalities resulting in gain of chromosome material					
8q	14%	14%	>30%	38%	>28%
11q	24%	22%	22%	40%	27%
21q	28%	25%	22%	25%	24%
22q	24%	19%	NR	17%	19%
1p	7%	8%	NR	25%	16%
9p	3%	14%	NR	18%	14%
13q	14%	6%	NR	15%	12%

Abbreviations: NR, not reported

^a Percentages for particular abnormalities calculated using only those studies that provided relevant data.

^bThis series includes 23 patients diagnosed with AML and 13 with myelodysplastic syndromes.

Table 2

Candidate genes located in recurrently lost or gained and/or amplified chromosome regions in AML patients with a complex karyotype

Candidate Genes		Chromosome location	Reference no.
Symbol	Name		
Loss			
<i>MLH1</i>	mutL homolog 1, colon cancer, nonpolyposis type 2 (E. coli)	3p22.3	39
<i>CTNNA1</i>	catenin (cadherin-associated protein), alpha 1, 102kDa	5q31.2	55
<i>ETV6</i>	ets variant gene 6 (TEL oncogene)	12p13	30,39
<i>CDKN1B</i>	cyclin-dependent kinase inhibitor 1B (p27, Kip1)	12p13.1-p12	39
<i>TRADD</i>	TNFRSF1A-associated via death domain	16q22	39
<i>CBFB</i>	core-binding factor, beta subunit	16q22.1	39
<i>TP53</i>	tumor protein p53 (Li-Fraumeni syndrome)	17p13.1	31,39,51–53
<i>NF1</i>	neurofibromin 1 (neurofibromatosis, von Recklinghausen disease, Watson disease)	17q11.2	39,56
<i>TCF4</i>	transcription factor 4	18q21.1	39
Gain and/or amplification			
<i>TNF</i>	tumor necrosis factor (TNF superfamily, member 2)	6p21.3	39
<i>PBX2</i>	pre-B-cell leukemia homeobox 2	6p21.32	39
<i>TRIB1</i>	tribbles homolog 1 (Drosophila)	8q24.1	39,44
<i>MYC</i>	v-myc myelocytomatosis viral oncogene homolog (avian)	8q24	22,25,39,79
<i>NSMCE2</i>	non-SMC element 2, MMS21 homolog (S. cerevisiae)	8q24.13	39
<i>JAK2</i>	Janus kinase 2 (a protein tyrosine kinase)	9p24	39
<i>GAB2</i>	GRB2-associated binding protein 2	11q13.4-q13.5	45
<i>MLL</i>	myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, Drosophila)	11q23.3	39,41,80–83
<i>DDX6</i>	DEAD (Asp-Glu-Ala-Asp) box polypeptide 6	11q23.3	39,41
<i>ETS1</i>	v-ets erythroblastosis virus E26 oncogene homolog 1 (avian)	11q23.3	25,39,41
<i>FLI1</i>	Friend leukemia virus integration 1	11q24.1-q24.3	39,41
<i>FGF6</i>	fibroblast growth factor 6	12p13	39
<i>CCND2</i>	cyclin D2	12p13	39
<i>FLT3</i>	fms-related tyrosine kinase 3	13q12	39
<i>PAN3</i>	PAN3 polyA specific ribonuclease subunit homolog (S. cerevisiae)	13q12.2	39
<i>CDX2</i>	caudal type homeobox 2	13q12.2	39,61
<i>IDI1</i>	inhibitor of DNA binding 1, dominant negative helix-loop-helix protein	20q11	39
<i>BCL2L1</i>	BCL2-like 1	20q11.21	39
<i>APP</i>	amyloid beta (A4) precursor protein (peptidase nexin-II, Alzheimer disease)	21q21.2	40
<i>ERG</i>	v-ets erythroblastosis virus E26 oncogene homolog (avian)	21q22.3	39,40
<i>ETS2</i>	v-ets erythroblastosis virus E26 oncogene homolog 2 (avian)	21q22.3	39,40
<i>BCR</i>	breakpoint cluster region	22q11.2	39
<i>CHEK2</i>	CHK2 checkpoint homolog (S. pombe)	22q12	39
<i>NF2</i>	neurofibromin 2 (merlin)	22q12.2	39

Clinical outcome of AML patients with complex karyotypes

Table 3

Reference ^a	Definition	No. of patients	Age range (median)	CR rate (95% CI)	RD	ED/HD	Complete remission		Relapse rate	Survival	
							Median duration (mo)	Probability ^b		Median duration (mo)	Probability ^b
OLDER ADULTS											
Farag (2006) ¹²	3	122	60–86 (68) ^c	25% (17–32)	50%	25%	—	3% (5y)	90%	—	2% (5y)
Fröhlings (2006) ¹¹	3	61	61–84 (67) ^c	10% (5–20)	62%	28%	—	0% (2y)	100%	3.1	4% (3y)
Schoch (2001) ⁴⁸	3	45	60–81 (68)	44%	38%	18%	6	11% (3y)	90%	8	6% (3y)
van der Holt (2006) ¹⁴	3	36	60–78 (67)	39% (23–57)	—	—	7	—	79%	5	6% (3y) 3% (5y)
Grimwade (2001) ⁵	5	145	44–91 (66) ^c	26%	56%	19%	—	9% (5y)	—	3.7	2% (5y)
Farag (2006) ¹²	5	94	60–86 (68) ^c	23%	49%	28%	5.9	0% (5y)	95%	2.6	0% (5y)
Fröhlings (2006) ¹¹	5	44	61–84 (67) ^c	7% (2–18)	68%	25%	—	0% (2y)	100%	2.7	3% (3y)
YOUNGER ADULTS											
Schoch (2001) ⁴⁸	3	45	19–59 (47)	47%	44%	9%	8	15% (3y)	71%	7	12% (3y)
Slovak (2000) ³	3 with -5/5q-/-7/7q-	33	17–54 (39) ^d	37% (19–54)	—	—	—	—	—	—	3% (2y)
Slovak (2000) ³	3 without -5/5q-/-7/7q-	30	17–54 (39) ^d	50% (31–69)	—	—	—	—	—	—	20% (2y)
ADULTS											
Haeflrich (2004) ⁷⁵	3	99	16–81 (58) ^c	35%	48%	17%	5	—	—	4	—
Visani (2001) ⁷⁶	4	106	15–83 ^c	35%	—	—	—	—	—	—	—
Byrd (2002) ⁶	3–4	36	15–86 (51) ^e	47%	—	—	—	12% (5y)	—	10	8% (5y)
Byrd (2002) ⁶	5	99	15–86 ^p (64) ^e	30%	—	—	—	3% (5y)	—	4	2% (5y)
YOUNGER ADULTS AND CHILDREN											
Grimwade (1998) ²	5	95	0–55 (34) ^e	67%	20%	13%	—	32% (5y)	—	—	21% (5y)
CHILDREN											
Stark (2004) ⁸	3 ^f	9	0–18 (6)	78%	—	—	—	67% (4y) ^g	—	—	36% (4y)
Betts (2007) ¹³	3	8	1–14 (3)	75%	—	—	11 ^h	—	83% ^h	16 ^h	19% (3y) ^h

Abbreviations: CR, complete remission; ED/HD, early death or hypoplastic death; —, not reported.

^aThe references column lists the first author and year of publication (in parentheses), followed by the superscript reference number.

^bThe number in parentheses indicates a time point (in years) at which the probability was determined.

^cAge range and median reported for all patients included in this study.

^dAge range and median reported for patients comprising the prognostically unfavorable category that also included patients with non-complex karyotype.

^eMedian age pertains to patients with a complex karyotype, but the age range is for all patients included in this study.

^fCategory defined as “miscellaneous 3 abnormalities”.

^g4-year event-free survival rate.

^hCalculated from data provided in Table 2 of this article. 13