

# Current views of chromosomal abnormalities in pediatric acute myeloid leukemia (AML)

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**Abstract.** – Chromosomal abnormalities are an attractive avenue for the screening of various disorders especially related to carcinogens like acute myeloid leukemia (AML). The cytogenetic findings like Karyotypic patterns are common in pediatric patients. On the other hand, monosomal karyotype (MK) and complex karyotype (CK) are more common in older patients. Further, recent studies have revealed direct proportion between the number of chromosome abnormalities and mortality rates in both pediatric as well as old patients affected by AML. Moreover, to be specific 5q, 7q and/or 17p loss lead to higher mortality rates in comparison to loss of to MK. The present review article would put light on current views of important chromosomal changes during AML, especially in pediatric patients.

Key Words:

Chromosome, AML, Pediatrics, Screening.

## Introduction

Clonal chromosomal abnormalities are seen in about 50-60% of patients with AML<sup>1-3</sup>. Normal karyotype (NK) AML is a very heterogeneous group where additional mutational analyses (FLT3-ITD, NPM1, CEBPA) are nowadays obligatory. There is an association of age and karyotype abnormalities in AML<sup>4</sup>. Chromosomal translocations, such as t(8;21), t(15;17), t(16;16) or inv<sup>16</sup> are usual in younger patients whereas deletion of chromosome 5 is more prevalent in patients older than 60 years<sup>5</sup>. Some scholars<sup>6</sup> proposed cytogenetic classification based on age and incidence according to the type of abnormalities, i.e. “deletional”, “translocational” or “trisomy” karyotype, but are controversial. Further, there is no proven correlation between chromosomal abnormalities and gender<sup>7</sup>. Moreover, there are several recurrent

abnormalities, like t(1;16)(p31;q24) with NFIA/CBFA2T3 fusion gene reported to be associated with acute erythroleukemia young infants<sup>8</sup>.

## Generally Accepted Cytogenetically High Risk AML

The incidence of complex karyotype increases with age, especially over the age of 60 and is more common in secondary AML. It confers poor prognosis with lower CR rate, and shorter DFS and OS. Complex karyotype is mostly based on the presence of deletions of chromosome 5 and 7 combined with other abnormalities<sup>9</sup>. There is a strong association between complex karyotype and mutation of the TP53 gene<sup>10</sup>. Rearrangements aberration is common in long arm of chromosome 3 whereas translocation is often observed in both the long arms of chromosomes 3 in 1.0-2.5% of AML cases<sup>11</sup>. Further, the inversion is more commonly observed in comparison to translocation<sup>7</sup>. On the other hand, WHO recognized entity involving RPN1-EVI1 genes (EVI1 gene now called MECOM) is commonly reported in pediatric patients<sup>12</sup>. Deletion of chromosome 7 is often an additional chromosome abnormality, like complex and monosomal karyotypes<sup>13</sup>. Data also support consideration of MDS with inv(3)(q21q26.2)/t(3;3)(q21;q26.2) as an AML with recurrent genetic abnormalities, irrespective of blast percentage<sup>14</sup>.

## Monosomy and Deletion of Chromosome 7

Monosomy of chromosome 7 could be isolated or found in the context of complex karyotype. Monosomy 7 and deletion of 7q are present as a single chromosomal alteration only in 35% and 33%, respectively, of all AML cases<sup>11</sup>. Although, the majority of the large leukemia study groups consider isolated deletion of chromosome 7q to

be a bad prognostic factor. Some groups (CAL-GB) suggested to be related to intermediate-risk AML<sup>9</sup>. Recurrent somatic mutations in CUX1, LUC7L2 and EZH2 genes are also recurrent in -7/del(7q)<sup>15</sup>. Also, AML patients with chromosome 7 aberrations are characterized by frequent multi-lineage dysplasia in bone marrow cells and poor clinical course with a low rate of CR (20-30%).

### **MLL**

Translocations involving 11q23/MLL are present in 5% of *de novo* AML and 10% of tAML (mostly previously treated with topoisomerase-II inhibitors)<sup>16</sup>. Moreover, there is an abundance of gene partners for MLL, as more than 65 have been described to date<sup>7</sup>. The most common translocations include t(9;11)(p21;q23), t(11;19)(q23;p13), 10p12/11q23-16 rearrangements, and t(6;11)(q27;q23). On the other hand, recent works showed that MLL-PTD (partial tandem duplications) did not have a prognostic impact in CN-AML patients treated with intensive therapy. Many patients still succumb to the disease and the course of disease is more dismal for the patients not eligible for intensive chemotherapy<sup>17-19</sup>. So, the new, as well as effective drugs targeting MLL, are entering into the early phase of clinical trials<sup>20,21</sup>.

### **Monosomy or Chromosome 5 Deletions**

The monosomy of chromosome 5 (-5) and deletion of the long arm of the chromosome 5 (5q-) has been observed to be 6-9% of all the chromosomal abnormalities during AML<sup>9</sup>. It often occurs in the patients older than 60 years and is rarely described as an isolated abnormality in AML. These chromosomal alterations are frequently observed in patients who were previously exposed to alkylating agent favoring multi-lineage dysplasia in bone marrow cells leading to secondary AML<sup>7</sup>. However, this is a very rare chromosomal abnormality (<1%)<sup>22</sup>. The affected patients are often children or young men (median 23-30 years) and the disease is presented as *de novo* AML or MDS. It predicts short survival and these patients are candidates for allogeneic stem cell transplantation<sup>7</sup>.

### **Not Generally Accepted Cytogenetically high-risk AML 17p Abnormalities**

The abnormalities under the above category are accepted as a marker for high-risk AML. These are described<sup>23</sup> as 17p deletion or add 17p, and are often a part of complex karyotype together

with abnormalities of chromosomes 5 and 7. They indicate a resistant disease with short survival and often involvement of tumor suppressor gene TP53<sup>24</sup>. Another abnormality that also leads to deletion of 17p is isochromosome 17q and is associated with a poor prognosis<sup>25</sup>. The well-known Philadelphia translocation is seen in <1% of AML<sup>26,27</sup>. Despite this, data in the literature are scarce. The patients' clinical features, cytogenetic abnormalities, molecular features and genome signature are different from those with CML<sup>28,29</sup>.

### **Trisomy 8**

This is the most common trisomy in AML. About 10% of all AML patients bear this abnormality<sup>7</sup>. All the international cooperative groups consider trisomy 8 as an intermediate cytogenetic-risk alteration<sup>30</sup>. It is frequent for all ages, but prevalence is higher in older age. Although individuals with a constitutional +8 mosaicism have an increased risk of AML, only a minority develops this disease. Secondly, there does not seem to be an increased risk of AML in CML patients with trisomy 8-positive/t(9;22)-negative clones emerging after treatment with imatinib<sup>31</sup>. Thirdly, the discriminating gene expression pattern of AML with isolated +8 does not depend on the up-regulation of chromosome 8 genes alone. In fact, array-based analyses have revealed several cryptic chromosome changes in AML with +8 as a seemingly sole change and mutations of the ASXL1, JAK2, and TET2 genes<sup>32-34</sup>.

### **Age-Dependent Incidence of Different Chromosomal Abnormalities**

The data from one population-based study clearly indicated that the age-dependent increase in incidence of AML substantially differs between the cases with balanced, with normal, and with unbalanced karyotypes. Further, it was suggested that mechanisms of leukemogenesis are different and more or less age-dependent<sup>35</sup>. Moreover, there are two different age profiles in AML from the cytogenetic point of view. The first one is characterized by a rather constant incidence over lifetime and is represented by balanced translocations. In contrast, unbalanced aberrations and especially complex aberrant karyotype show a sharp increase in incidence in older age. This is suggestive of different mechanisms in the underlying pathogenesis of AML<sup>35</sup>. At least a proportion of, if not all, balanced translocations of pediatric leukemias already develop in the prenatal period. This was demonstrated by the observation of twins developing

acute leukemia with reciprocal gene fusions, e.g. cALL with TEL-AML1<sup>36</sup>. The retrospective polymerase chain reaction analyses of Guthrie cards of children led to the detection of clonotypic sequences of the respective gene fusions AML1-ETO, PML-RARA, and CFBF-MYH11<sup>36</sup>. On the other hand, unbalanced aberrations lead to genomic imbalances and might occur due to a variety of mechanisms, including sister chromatid exchange of ring chromosomes, unbalanced distribution of the chromosomes to the daughter cells, or incorrect repair of DNA double-strand breaks<sup>37-39</sup>. These genetic alterations seem to occur more frequently in aging cells due to shortening of telomeres and less efficient DNA repair capacity. The age-specific distribution of the molecular markers might be due to age-specific changes in hematopoiesis and to changes in the available pools of hematopoietic precursors as targets for leukemogenesis. Different age profiles of the cytogenetic subtypes and of the recurrent molecular markers indicated different mechanisms of the pathogenesis of AML<sup>35</sup>. WHO classification from 2008 roughly separates AML into three categories: *de novo* AML, therapy-related AML and secondary AML (with antecedent MDS or MPN). These categories seem to have a different ontogenesis and age-distribution<sup>40</sup>. There is accumulating data about the time sequence of events that lead to overt leukemia, where specific gene mutations and even CBFH/MYH translocation in *inv*<sup>16</sup> occur in preleukemic stem cells. These findings indicated that preleukemic HSCs could survive induction chemotherapy. Cytogenetic data from the Swedish Acute Leukemia Registry could also provide insight into the clonal origin and evolution, especially in the cases with complex karyotype<sup>41-43</sup>.

### Failures in Cytogenetics

Unsuccessful (UC) and unperformed cytogenetics (UPC) are often reported together as a “not determined karyotype”<sup>44</sup>. The definition of unsuccessful cytogenetic karyotype (UC) is a lack of analyzable metaphasis. There are several possible explanations for this phenomenon. Some cases with UC are undoubtedly due to insufficient number of cells in the bone marrow aspirates sent for cytogenetic analysis. Furthermore, human errors in taking the bone marrow aspirates cannot be excluded, such as too small volumes or diluting the bone marrow cells with peripheral blood, and technical problems in the laboratory. Finally, there might be some biological explanations for UC, representing the intrinsic properties of the leukemic

clone, such as inability to divide *in vitro*. In fact, UC is not specific for AML. There are reports of dismal prognosis of ALL cases with UC as well as of myelodysplastic syndromes with UC<sup>45,46</sup> with the latter suggesting that UC is a property of dysfunctional stem cells.

### Unperformed Cytogenetics

The issue of unperformed karyotype is even more controversial than unsuccessful karyotype. This group is almost invisible in the literature, since karyotype is usually mandatory in clinical trials. UPC is often lumped together with unsuccessful karyotype or just classified as not done, not available or not determined<sup>44</sup>. The population-based AML Registry is an excellent source to identify such a patient group. It is impossible in retrospect to know the reasons why the karyotype was performed or not from case to case, but it is likely that many were not fit for intensive treatment. The presence of UPC emphasizes the need for proper genetic analyses of all patients for whom treatment with curative intent is planned, and even in the cases where therapy is not planned to have data for future analysis.

### Conclusions

Chromosomal aberrations are crucial especially in the cases of pediatric acute myeloid leukemia (AML). Proper screening of these chromosomal aberrations warrants effective management of AML.

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### Conflict of interest

The authors declare no conflicts of interest.

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