Secondary Chromosomal Abnormalities of de novo Acute Myeloid Leukemia - A First Report from the Middle East

Abolfazl Movafagh¹, Abbas Hajifathali², Mahdi Zamani¹

Abstract

Secondary chromosome aberrations in de novo acute myeloid leukemia (AML) are less specific and occur in addition to the primary chromosome abnormalities. Secondary chromosome aberration in acute nonlymphocytic leukemia has been recognized for many years as the most serious long-term complication of malignant disease. Our aim in this study was to focus on patients with AML associated with secondary chromosomal abnormalities in 127 consecutive Iranian leukemia patients. Methotrexate (MTX) cell synchronization and 24h non-stimulated cultures of bone marrow cells were applied to determine the incidence of chromosomal aberrations and association of specific primary and secondary chromosome anomalies according to French American British (FAB) morphological subtypes. The distribution of the secondary changes was clearly non-random. The most frequent numerical changes were -X, -Y, -7, +8 , -10 and +22 and the most common structural aberrations were i(17q), 9q-, dicentric and marker chromosome. We believe this report is the first for de novo AML patients showing secondary chromosomal abnormalities which are quite non-random. The findings could contribute to widening knowledge of related chromosomal abnormalities.

Keywords: Acute myeloid leukemia - chromosomes - secondary abnormalities - Iran - Middle East
Abnormalities in AML

Figure 1. The Major Secondary Chromosome Abnormalities in AML

<table>
<thead>
<tr>
<th>Primary</th>
<th>Chromosome number</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(9q; 22q)</td>
<td>dup</td>
</tr>
<tr>
<td>n=28</td>
<td>1</td>
</tr>
<tr>
<td>t(8q; 21q)</td>
<td>1t 2del 1t 3+ 2del</td>
</tr>
<tr>
<td>n=35</td>
<td>1r inv 1- 1- 1- 1t 7- 2- 2</td>
</tr>
<tr>
<td>t(15q; 17q)</td>
<td>1brk 1del 1dic 1trl 9+ 1del 2del 1del</td>
</tr>
<tr>
<td>n=30</td>
<td>1del 1i 2- 1t 1tr 1dic 1- 2</td>
</tr>
<tr>
<td>del(20q)</td>
<td>1+</td>
</tr>
<tr>
<td>n=5</td>
<td>1del 1</td>
</tr>
</tbody>
</table>

where t, gain of chromosome; -, loss of chromosome; t, translocation; del, deletion; der, derivative chromosome; dup, duplication; I, isochromosome; inv, inversion; v, ring chromosome; mar, markers chromosome; break, brk, dicentric; dic

was detectable among the additional abnormalities in the remaining 12 patients (42.8%). Monosomy 7 and trisomy 8 were the most frequent numerical changes, each occurring in more than 10% of the cases (see Figure 1). An extra Ph marker was the most common structural aberration.

This research work for patients with M1 and M2 and t(8;21) yielded 35 (27.5%) cases, with approximately additional aberrations in 19 (54.2%) cases. These secondary changes were striking non-random, not only had approximately 75% of the patients with additional abnormalities lost one or both sex chromosome, but the excess of 9q deletion (9%) was also very conspicuous. The only numerical autosomal aberration consistently seen was trisomy 8, present in 2 (8.2%) of the cases.

Translocation 15;17 is found exclusively in acute promyelocytic leukemia (M3), co-expression of t(8;21) and t(15;17) associated with break in chromosome 2P arm, dic (X) (q24), dic(5)(q22) , del(10) (q11), and del (11)(q23), -20. Trisomy 8 was the only common numerical change in this subgroup of ANLL. Most frequent structural secondary aberrations encountered in this group were del(7q), del(9q), and i(17q).

Secondary aberrations were ascertained in only 3 (9.4%) ANLL patients with t(9;11). However, even with these small numbers, the preponderance of trisomy 8 was striking.

An inversion/deletion of chromosome 16 was found in 9.4% of 12 ANLL patients, with additional aberrations detectable in 7(58%). Trisomy 8 was clearly the most frequent numerical secondary in 2 (16.6%) with these 6 AML patients. Chromosomes 7,8,9,15,16,17,21 / X,Y were the autosomes / sex chromosome most frequently preferentially affected in ANLL. The overall percentage of abnormal cells recorded within the range of 30 – 100% with various sub-group of the FAB classification in AML patients. Seventeen cases were not available for karyotyping, because of a lack of mitoses or inappropriate preparations, hence were excluded from this research work.

Discussion

In the light of these findings, and characteristic cytogenetic abnormalities which will be discussed in the following sections, specific structure and numerical changes detected in de novo AML have rarely been detected in secondary AML (Davies et al., 1988). One of the common translocation identified in leukemia is between chromosome 8q22 and chromosome 21q22 (Pei et al., 2008). It is associated with nearly 40% of cases of FAB-M2 AML and 8% to 20% of all cases of AML. M1 and, more rarely in AML M0, M4, M5, and other myeloproliferative syndrome (Luke et al., 2007). Sex chromosome loss occurred almost exclusively in patients with t (8;21), who also tended to have del (9) and/or trisomy 8 (Pedersen – Bjergaard, 1985; Heim and Mitelman, 1986; Luke et al., 2007). Observations similar to those we have made in this series following t(8;21) have also been reported in patients with AML. In this study, we confirmed that the lost of sex chromosome and del(9q) were common, in (75%) and (9%) cases, respectively.

The Philadelphia (Ph) chromosome, or t(9;22) is the hallmark of Chronic Myelogenous Leukemia (CML) (Cian Ciuilli et al., 2010), it results in juxtaposition of the 5′ part of BCR gene on chromosome 22 to the 3′ part of the ABL gene on chromosome 9 (Pei et al., 2008). Additional chromosome abnormalities occur in less than 10% of cases at diagnosis of Ph-positive chronic myelogenous leukemia (Arranz et al., 2002; Wang et al., 2004; Jeddi et al., 2008; Al Achkar et al., 2010; Karakosta et al., 2010). Several chromosomal abnormalities seem to be closely associated with the appearance of a secondary Ph22 often +8 , -7, and/or +Ph (Heim and Mitelman, 1986; Jeddi et al., 2008). Alternatively, genetic instability may cause the development of the 7q- in a karyotypically normal
cell, and the 7q- may be one of secondary changes that develop during tumor progression (Pedersen-Bjergaard, 1985). Our findings with secondary chromosome changes for t(9;22) almost is similar with others findings elsewhere (Chen et al., 1998).

Translocation 15;17 is found exclusively in acute promyelocytic leukemia (M3) (Park et al., 2008). It is well documented that some leukemia specific chromosome rearrangements such as inv(3), t(5;17), and inv(16), which used to be considered primary changes in the genesis of leukemia could also appear as secondary anomalies in the progression of the disease (Wetzer et al., 2004; Sakai et al., 2006). Co-expression of t(8;21) and t(15;17) associated with break in chromosome 2P arm, dic(X) (q24), dic(5) (q22), del(10) (q11), del (11) , (q23), -20 (Movafagh et al., 2009). Trisomy 8 was the only common numerical change in this subgroup of ANLL. Most frequent structural secondary aberrations encountered in this group were i(17q). Secondary aberrations were ascertained in only 12 (9.4%) AML patients with t(9;11), however, even with those small numbers, the preponderance of trisomy 8 was striking (Pedersen-Bjergaard, 1985; Johanssen et al., 2004).

An inversion / deletion of chromosome 16 was found in (9.4%) of 12 ANLL patients, with additional aberrations detectable in 4(33.3%) patients. Trisomy 8 was clearly the most frequent numerical secondary chromosomal abnormalities detected with these 12 AML patients. Chromosomes 7,8,9,15,16,17,21/X,Y were the autosomes/sex chromosome most frequently preferentially affected in our ANLL patients.

In summary, the information provided in this study (Table 1) demonstrated that the distribution of secondary chromosomal aberrations in our AML patients is quite non-random.

References