RESEARCH COMMUNICATION

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

Abolfazl Movafagh[1*], Abbas Hajifathali[2], Mahdi Zamani[1]

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

Asian Pacific J Cancer Prev, **12**, 2991-2994

Introduction

Specific structural changes detected in de novo AML have rarely been detected in secondary AML (Davies et al., 1988). However, certain secondary chromosomal abnormalities are associated with phenotypic feature of neoplastic cells where as primary chromosomal abnormalities maintain their essential biological characteristics (Johanssen et al., 2004; Sakai et al., 2006). A Secondary chromosomal abnormalities is generally considered strongly associated with the disease phenotype (Johanssen et al., 2004), examples of such secondary chromosomal abnormalities include the AML is well established in the current literature (Johanssen et al., 2004; Jung et al., 2008).

Secondary chromosomal abnormalities are less specific and occur in an addition to the primary abnormalities (Fourth International workshop on chromosome in Leukemia 2004; Batzio et al., 2009; Cho et al., 2010). Furthermore, secondary chromosomal aberrations reported in the literature were surveyed in AML with one of the following primary abnormalities: t(1;3), t(1;22), der(1;7), inv(3), t(3;5)+4, del(5q), t(6;9), -7, t(7;11), del(7q), +8 , t(8;16), t(8;21), +9, t(9;11), del(9q), t(9;22), +11, del(11q), t(11;19), del(12p) , +13, t(15;17), inv(16), t(16;21), i(17)(q10), del(20q), -21, +21, +22, and –Y (Johanssen et al., 2004; Jung et al., 2008; Shin et al., 2009). Our aim of this pilot study was one that focused on patients with AML associated with secondary chromosomal abnormalities in an Iranian populations.

Materials and Methods

During the last ten years, chromosome banding studies were performed on 127 unselected consecutive either adults sex patients with de novo AML admitted to the major referral hospitals affiliated of Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Bone marrow and peripheral culture, standard Methotrexate (MTX) cell synchronization procedures for cultures, collection of samples, and slide preparation were modified and performed in our laboratory (Misawa et al., 1988; Shaffer and Slovak, 2009). Chromosomes were analyzed with GTG banding, and the karyotypes were described in accordance with the 2009 International System of Human Cytogenetic Nomenclature (ISCN) (Brothman et al., 2009).

Results

On the basis of association of specific chromosomal changes with morphologic subtype, patients have been classified cytogenetically into various subtypes e.g. French American British (FAB) (Bennett et al., 1985). Among patients with AML , t(9;22) was found in 26 cases, in 92% as the only change . A clearly nonrandom pattern

*[1]Department of Medical Genetics, [2]Department of Internal Medicine, Oncology, Hematology, Cancer research Centre, Shahid Beheshti University of Medical Sciences, Tehran, Iran *For correspondence: Movafagh_a@yahoo.com*

Table 1. Secondary Chromosome Aberrations in ANLL

Primary	Chromosome number																							
rearrangement	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	X	Y	mar
t(9q; 22q) n=28	1dup				1-		11-	9+		1del	1+		1+	1t	1t		1t	1-	1+	1t	1+	2del	2+	1-	1
t(8q; 21q) n=35		1t	2del	1t 1del				3+	2del 1t						1r	1inv			1-	1-	1- 1t	1t 1der	7-	2-	2
t(15q; 17q) n=30		1	brk	1del 1dic	1dic		1tr 1del	9+	1del	2del	1del				1del		1i			2-	1tr	1-	1dic	1-	2
Inv(16) n=12		1-						2+								3del									1
t(9p;11q) n=3								2+																	
del (20q) n=5								1+										1del							1

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 that 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 and 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

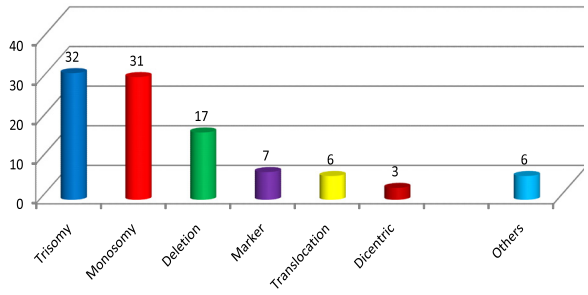

Figure 1. The Major Secondary Chromosome Abnormalities in AML

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 Myelogenious Leukemia (CML) (Cian Ciulli 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 (Wetzler 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

Al Achkar W, Wafa A, Mkrtchyan H, et al (2010). A rare case of chronic myeloid leukemia with secondary chromosomal changes including partial trisomy 17q21 to 17qter and partial monosomy of 16p13.3. *Mol Cytogenet*, **3**, 6-13.

Arranz E, Gil-Fernández JJ, Ramiro S, et al (2002). Deletion of sequences flanking the t(9;22) breakpoint: a secondary genetic event associated with loss of cytogenetic response to interferon in a Philadelphia-positive chronic myeloid leukaemia patient. *Br J Haematol*, **117**, 617-9.

Batzio SC, Hayes LA, He SZ, et al (2009). Secondary clonal cytogenetic abnormalities following successful treatment of acute promyelocytic leukemia. *AMJ Hematol*, **84**, 715-9.

Bennett JM, Catovsky D, Denial ML (1985). Proposed revised criteria for the classification of acute myeloid leukemia. *Ann Intern Med*, **103**, 620-5.

Brothman AR, Persons DL, Shaffer LG (2009). Nomenclature evolution changes in the ISCN from the 2005 to the 2009 edition. *Cytogenet Genome Res*, **127**, 1-4.

Chen Z, Morgen R, Mathilda N(1998). The Philadelphia Chromosome as a secondary Change in leukemia: Three case reports and an overview of the literature. *Cancer Genet Cytogenet*, **101**, 148-51.

Cho BS, Kim HJ, Eom KS, et al (2010). A case report of the second de novo acute myeloid leukemia (AML) following allogenetic stem cell transplantation in a patient with the first AML. *J Korean Intern Med*, **25**, 110-3.

CianCiulli M , Dalsass A , Douti E , et al (2010). Chromosome abnormalities additional to the philadelphia chromosome at the diagnosis of chronic myelogenous leukemia: Pathogenesis and prognostic implications. *Cancer Genet Cytogenet*, **199**, 76-80.

Davies SV, Murray JA , Bowser – Reiley SM, et al (1988). Secondary leukemia with a translocation (8;21). *Cancer Genet Cytogenet*, **31**, 271-4.

Fourth International workshop on chromosome in Leukemia (2004). Secondary leukemia associated with neoplasia. *Cancer Genet Cytogene*, **11**, 319-24.

Heim S, Mitelman F (1986). Secondary chromosome aberrations in the acute leukemias. *Cancer Genet Cytogenet*, **22**, 331-8.

Jeddi R, Gouider E, Benneji H, et al (2008). Secondary chronic myelomonocytic leukemia with monosomy 7 after successful treatment of acute promyelocytic leukemia. *Pathologie Biologie*, **56**, 162-3.

Johanssen B, Mertens F, Mitelman F (1994). Secondary chromosomal abnormalities in acute leukemias. *Leukemia*, **8**, 953-62.

Jung SI, Cho HS, Lee CH, et al (2008). Two cases of trisomy 19 as a sole chromosomal abnormality in myeloid disorders. *Korean J Lab Med*, **28**, 174-8.

Karakosta M, Voulgarelis M, Vlachadami I, et al (2010). Translocation (6;13) (p21;q14.1) as a rare nonrandom cytogenetic abnormality in chronic lymphocytic leukemia. *Cancer Genet Cytogenet*, **198**, 66-70.

Luke F, Peterson, Boyapal A , et al (2007). Acute myeloid leukemia with the 8;21 translocation: Secondary mutational events and alternative t(8;21) transcripts. *Blood*, **110**, 799-805 .

Misawa S, Horiike S, Taniwaki M (1988). Detection of karyotypic abnormalities in most patients with APL by adding ethidium bromide to short term culture. *Leuk Res*, **12**, 719-29.

Movafagh A, Hajifathali A, Isfahani F, et al (2009). Geographic heterogeneity of cytogenetic characteristics of acute myeloid leukemia in the early detection: A comparative study of Iranian and Indian adult patients. *IJCP*, **2**, 85-9.

Park TS, Choi JR, Yoon SH, et al (2008). Acute promyelocytic lekemia replacing as secondary acute myelogeneous leukemia with translocation t(3;21) (q26;q22) and RUNX1-MDS1-EVIY fusion transcript. *Cancer Genet Cytogenet*, **187**, 61-73.

Pedersen-Bjergaard J (1985). Incidence, previous treatment and chromosome characteristics of secondary acute nonlymphocytic leukemia. *Cancer Treat Rev*, **12**, 65-75.

Pei L, Lei C, Rajyalakshmi L, et al (2008). Acute myeloid Leukemia harboring t(8;21) a heterogeneous disease with poor out – come in a subset of patients unrelated to secondary cytogenetic aberrations. *Modern Pathology*, **21**, 1029-36.

Sakai R, Fujimaki K, Yamazaki E, et al (2006). Acute Myelomonocytic leukemia with dysplastic bone marrow eosinophils showing t(15;17) and a secondary chromosomal aberration , inv(16). *Int J Hematology,* **84**, 417-20.

Shaffer LG, Slovak ML, Campbell LJ, (editors) (2009). An International System for Human Cytogenetic Nomenclature. Basel: S. Karger.

Shin SY, Koo SH, Kwon KC, et al (2009). Chromosome 8 pentasomy with partial tandem duplication of 11q23 in a case of de novo acute myeloid leukemia. *Cancer Genet Cytogenet*, **194**, 44-7.

Wang Y, Hopwood VL, Hu P, et al (2004). Determination of secondary chromosomal aberrations of chronic myelocytic leukemia. *Cancer Genet Cytogenet*, **153**, 53-6.

Wetzler M, Dodge RK, Mrózek K, et al (2004). Additional cytogenetic abnormalities in adults with philadelphia chromosome-positive acute lymphoblastic leukaemia: A study of the cancer and leukaemia group B. *Br J Haematol*, **124**, 275-88.