International Journal of Research in Medical Sciences
Vaniawala SN et al. Int J Res Med Sci. 2017 Jun;5(6):2652-2656
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20172464

Original Research Article

The possible significance of trisomy 8 in acute myeloid leukemia

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Received: 04 April 2017
Accepted: 03 May 2017

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ABSTRACT

Background: Acute myeloid leukemia (AML) is a heterogeneous disorder that results from a block in the differentiation of haematopoietic progenitor cells along with uncontrolled proliferation. Trisomy 8 is the most common recurring numerical chromosomal aberrations in acute myeloid leukemia (AML). It occurs either as a sole anomaly or together with other additional chromosomal aberrations. The prognostic significance of trisomy 8 in presence of other additional chromosomal abnormality depends on clonal cytogenetic changes. The patients with trisomy 8 had shorter survival with significantly increased risk with other chromosomal abnormality.
Methods: Total 139 patients were screened between January 2016 to November 2016 who were suspected of AML cases. Bone marrow cultures were set up using conventional cytogenetic methods. Chromosomal preparation was made and subjected to GTG banding technique. Banded metaphases were analysed and karyotyped for further analysis.
Results: Cytogenetic evaluation of karyotyped of 139 suspected AML patients showed 52 with t(8;21)(q22;q22), 36 with t(15;17)(q22;q12), and 11 with inv(16)(p13;q22). The rest 40 cases found with additional chromosomal abnormalities, of which 16 were sole trisomy 8 and 24 cases were found with other chromosomal abnormalities In addition, only one person found with t(8;21) and trisomy 8, while three person having t(15;17) with trisomy 8.
Conclusions: AML is considered to be one of the most important cytogenetic prognostic determinants. Recurrent chromosomal translocation with trisomy 8 varying 1.9% for t(8;21) and 8.3% for t(15;17). In the present study trisomy 8 in AML with known favourable anomalies is very small. Therefore, it cannot be taken as a prognostic marker.

Keywords: AML, Cytogenetic, Karyotype, Prognosis, Trisomy 8

INTRODUCTION

Cytogenetic studies in AML become most important useful prognostic factor in predicting initial response to induction chemotherapy, remission and overall survival.[1] Trisomy 8 is recurring numerical chromosomal aberrations in acute myeloid leukemia (AML). It occurs either as a sole anomaly or together with other aberrations. Furthermore, identification of primary translocations and inversions have trisomy 8 as a secondary abnormality includes t(8;21), t(9;11), t(15;17), and inv(16), which may have a good or intermediate prognosis. Thus, absence of this identification can confound interpretation of the prognostic significance of trisomy 8.[2]

The leukemic karyotype specially with AML can be used as prognostic factor in predicating the initial response to induction of therapy, remission and overall survival because exact genetic and reliable method required to

enable risk assessment.[3] The World health organization (WHO) in 2008 revised its classification to recognize impact of molecular marker on prognosis with normal cytogenetic findings. Furthermore, the diagnostic and prognostic testing of bone marrow is important to predict the outcomes.[4] However, the cytogenetic study is important to confirm the wide variety of common, rare, novel chromosomal translocations in patients with haematopoietic disorders which provide valuable diagnostic and prognostic information.[5]

In fact, patients with trisomy 8 had a shorter survival which significantly increased the risk for leukemic transformation than patients with other chromosomal rearrangements. Thus, the karyotype of leukemic blast has been shown prognostic determinants for AML. Moreover, the survival was poor when a high proportion of mitotic cells were trisomic in nature.[6]

Paulsson et al, have reported that the AML with trisomy 8 as sole aberration is still not clear whether trisomy 8 is primary event leading to AML or not.[7] Moreover, there was no cryptic rearrangements or mutations found to support the hypothesis of trisomy 8. Virtaneva et al and Schoch et al, suggest that the gene expression experiments do support the idea that overexpression of gene on chromosome 8 is involved in the development of AML.[8,9] Thus, trisomy 8 as a sole aberration should still cytogenetic entity.

Pedersen et al, suggested that the wide variety of haematological diseases associated trisomy 8 shows the aberration is not related to any pathogenesis, as it is mechanism that driving progression of malignant and premalignant conditions of myeloid haematopoietic system.[10] Schaich et al, have reported that the unclear prognostic situation specially with AML accompanied by therapeutic situation.[11]

In the present study we describe the possible role of trisomy 8 in AML, as it is an important prognostic marker in management of AML along with recognition of specific subtypes. We also report, the prognostic significance of trisomy 8 accompanying with other additional chromosomal abnormalities.

METHODS

A total of 139 AML suspected Patients were screened between January 2016 to November 2016. Conventional Cytogenetic technique was performed on 24 hours unstimulated short term culture of bone marrow cells. The cells were grown in culture medium Marrow Max (GIBCO) supplemented with 20% of Fetal Bovine Serum (FBS). The colcemid was added for 30 minutes followed by KCL (75 mM) at room temperature for 27 min and carnoy's fixative for four times. Slides were stained with giemsa trypsin giemsa (GTG) banding technique. GTG banded metaphases from each culture were analysed and karyotyped by using automatic IKROS karyotyping software. The karyotypes were described according to International system for human cytogenetic nomenclature.[12]

RESULTS

In the present investigation a total of 139 AML suspected patients were studied. The abnormal karyotypes with known chromosomal translocation are shown in Figure 1 and 2. All 139 patients were diagnosed with conventional cytogenetic. Of which, 52 (37.4%) were found with t(8;21)(q22;q22), 36 (25.8%) with t(15;17)(q22;q12), 11(7.91%) with inv(16)(p13;q22), and 40 (28.7%) had other additional chromosomal abnormalities shown in Figure 3.

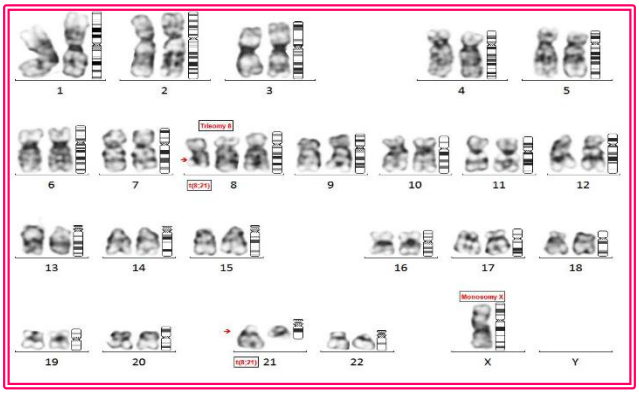

Figure 1: G-banded karyotype of female AML patient showing t(8;21)(q22;q22) with trisomy 8 and monosomy X.

In addition, 40 other additional chromosomal abnormalities, of which 16 (40%) were found having sole trisomy 8 and rest of 24 (60%) were found having other additional abnormalities. Further analysis showed that out of 52 t(8;21), only one person (1.9%) was having trisomy 8 with translocation t(8;21). On the other hand, in t(15;17), only 3 patients (8.3%) were found having trisomy 8 with translocation t(15;17) shown in Figure 4. Results suggest that the frequency of trisomy 8 in AML along with known translocation is very small.

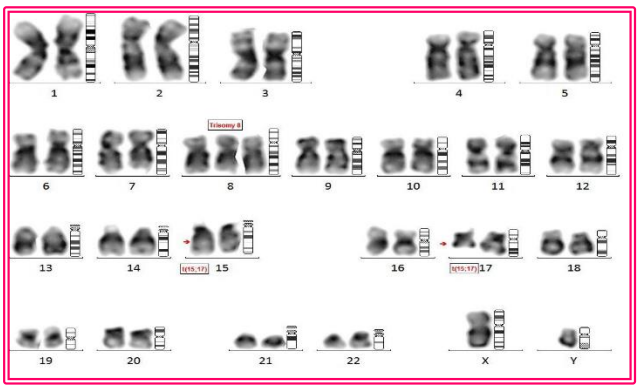

Figure 2: G-banded karyotype of male AML patient showing t(15;17)(q22;q12)with trisomy 8.

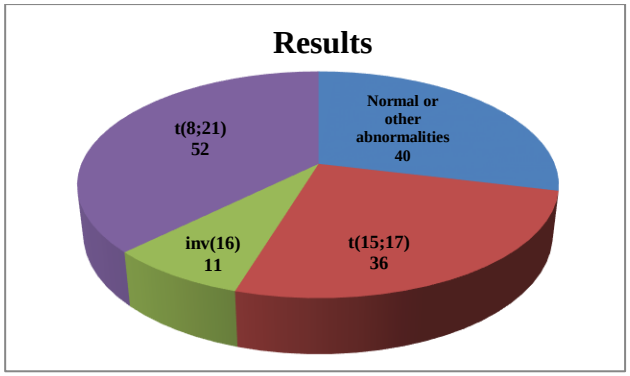

Figure 3: Frequency of chromosomal aberrations found in AML.

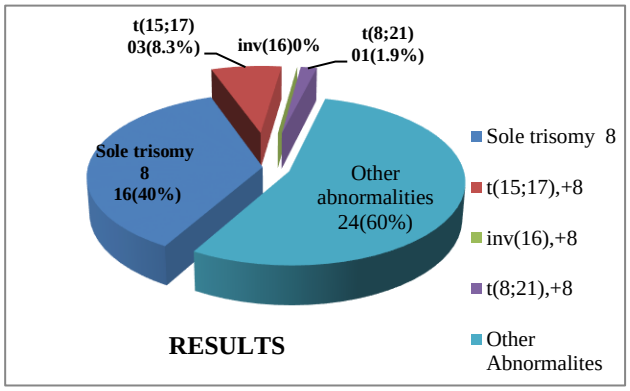

Figure 4: Frequency of trisomy 8 along with common translocations found in AML.

The results of dual colour FISH analysis using AML1 and ETO probes are shown in Figure 5. It clearly shows two fusions with red and green signals of AML1/ETO conforming the t(8;21), while using PML and RARA probes, Figure 6 showed two fusions with red, green, yellow indicating t(15;17). Interstitial FISH analysis using inv(16) shown in Figure 7, which shows fusion of red and green signals in one which is normal chromosome #16 and separate green and red signals indicating inv(16) chromosome.

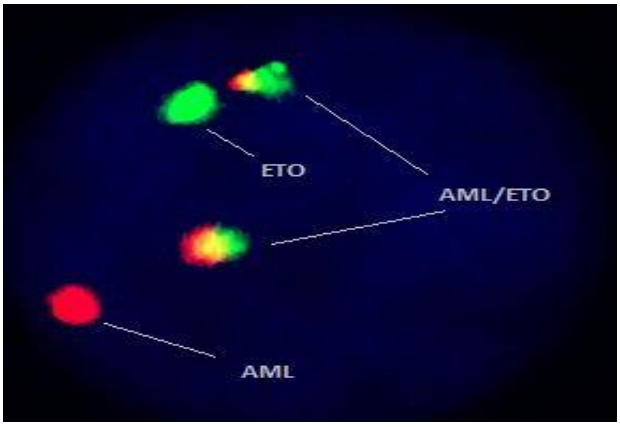

Figure 5: FISH analysis showing AML1/ETO (red and green) fusion signal [t(8;21)].

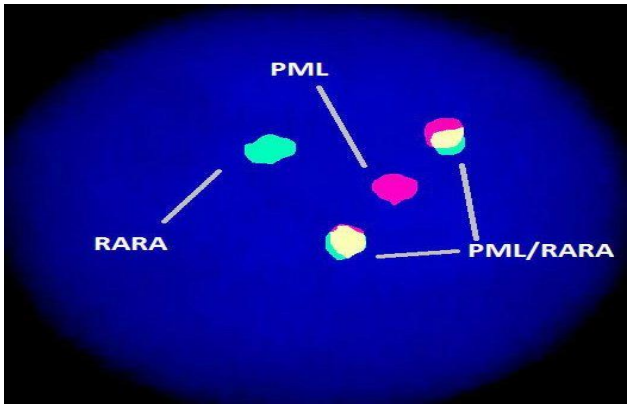

Figure 6: FISH analysis showing PML/RARA (green, red and yellow) fusion signal [t(15;17)].

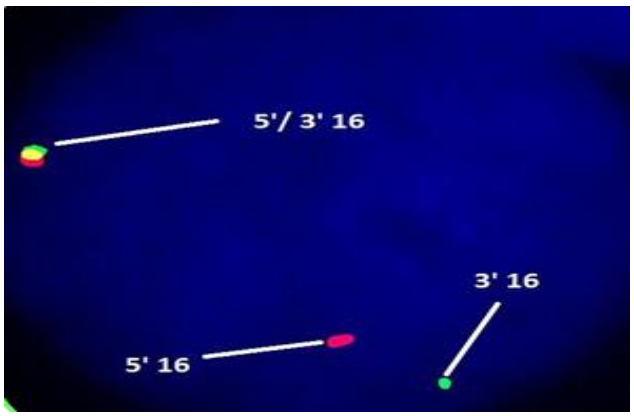

Figure 7: FISH analysis showing one green and red fusion normal 16 and separate green and red signals indicate inv(16) chromosome.

DISCUSSION

Cytogenetic analysis play a critical role in prognosis, classification, diagnosis and management of acute myeloid leukemia (AML). It has become an essential technique that helps doctors to identify the leukemia and provide treatment guidance.

In AML, chromosomal abnormality classified as structural or numerical. Structural abnormality can be defined as disturbances in normal composition of chromosome. While numerical abnormalities represent significant proportion of chromosomal number change found in humans. Certain specific chromosomal abnormalities have been identified in AML, which are closely associated with morphological and clinical subset of this disease.[3]

The aim of the study was to evaluate the prognostic significance of trisomy 8 accompanying with other chromosomal abnormality. Moreover, in AML occurrence of trisomy 8 is associated with malignant and premalignant condition of myeloid haematopoietic system.[10] Thus, in trisomy 8 occurance of malignant conditions raising the possibility of constitutional mosaic

trisomy 8.[13] It was reported that AML +8 alone associated with either intermediate or poor prognosis.[1,14]

In, AML there is some evidence suggest that the patients with trisomy 8 occuring together with other additional chromosomal abnormalities have the prognosis confirmed by accompanying with aberration. On the other hand,Schlenk et al and De Botton et al reported that the favourable prognosis [t(8;21),t(15;17), and inv(16)] of patients was not basically changed by an addition to trisomy 8.[15,16]

Furthermore, Said et al suggest that in AML trisomy 8 coexits with other neumerical chromosomal abnormalities which is around 16%, while Sen et al reported that the significant proportion of patients with trisomy 8 presents with extramedullary diseases.[17,18] In addition, extra chromosome 8 does not affect the expression of apoptosis regulatory gene which is located on chromosome 8.[8]

CONCLUSION

In conclusion, it is significant to discuss between patients with trisomy 8 as the sole cytogenetic abnormality or patients with trisomy 8 in combination with favourable aberrations. In the present study, total 139 AML suspected patients were studied. Recurrent chromosomal translocations with trisomy 8 were varying between 1.9% for t(8;21), 8.3% for t(15;17) and 40% were found having +8 as a sole aberration. Trisomy 8 in AML with known favourable anomaly is very small. Therefore, it cannot be considered as a prognostic marker.

ACKNOWLEDGEMENTS

Authors wish to thank technical assistance provided by cytogenetic unit.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Vaniawala SN, Patel MV, Chavda PD, Zaveri SH, Gadhia PK. The possible significance of trisomy 8 in acute myeloid leukemia. Int J Res Med Sci 2017;5:2652-6.