Archives of Hematology and Blood Diseases

ISSN: 2639-3581

Volume 1, Issue 2, 2018, PP: 08-14

Assessment of Prognostic Significance of Monosomy 7 in Myeloid Malignancies Sole or with Recurrent Chromosomal Abnormalities: An Indian Experience

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Abstract

Clonal disorders that are characterized by acquired somatic mutations in hematopoietic progenitors are generally observed in myeloid malignancies. Recent advances in understanding of the genetic basis of myeloid malignancies have provided important insights into the pathogenesis of Acute Myeloid Leukemia (AML) and Myeloproliferative Diseases (MPD) and have led to the development of novel therapeutic approaches. Monosomy 7 or partial deletion of the long arm of chromosome 7 (7q-) is a frequent cytogenetic finding in the bone marrow of patients with Myelodysplasia and AML being found in about 40% of patients. In contrast, -7 or deletion of the long arm of chromosome 7 [del(7q)] is found in only 4% to 5% of pediatric patients with AML. In this research article we are reporting 12 patients with monosomy 7 in hematologic malignancies. Total 12 patients were studied using conventional cytogenetic and Fluoresence in Situ Hybridization techniques. From 12 patients, 6 patients with AML diagnosis, 4 with Chronic Myelomonocytic Leukemia (CML) and 2 were with Juvenile Myelomonocytic Leukemia (JMML). Out of all 12 patients, 10 patients expired within 3-6 months of diagnosis. Based on our results, we concluded that monosomy 7 along with other cytogentic changes shows poor prognosis.

Keywords: *7/del7q, monosomy 7, deletion 7, FISH, Myeloid Leukemia*

Introduction

Leukemia is characterized by presence of number of non random chromosome abnormalities. Molecular characterization of these abnormalities focused on specific genes implicated in the process of leuke mogenesis. Chromosomal aberrations have been correlated with specific laboratory and clinical characteristic and are now being used as diagnostic and prognostic markers directing the selection of therapies. Specific chromosome aberrations and their molecular counterparts have been included in the World Health Organization classification of hematologic malignancies, and together with morphology, immunophenotype and clinical features are used to define distinct disease entities. It is necessary to find out the prognostic significance of the primary and secondary aberrations in Leukemia [Mrozek 2004].

Preleukemic Myelodysplastic syndrome, AML in children and de novo and therapy-related Myelodysplastic syndrome (MDS) and AML in adults shows complete or partial loss of chromosome 7. Predominantly monosomy 7 or deletions of 7q, are associated with a variety of myeloid disorder which is associated with poor prognosis [**N A** Heerema et al, 2004**].**

Monosomy 7 is one of the most recurrent chromosome alterations observed in patients with MDS and AML, and it may also be found cover up to the Philadelphia chromosome in Chronic Myelocytic Leukaemia (CML) in accelerated or blastic phase. It is even more common in secondary MDS/AML, and is associated with a

variety of Mendelian and non-Mendelian predisposing disorders or in the so-called monosomy-7 families, where it recurs in subjects developing MDS/AML. Also partial monosomy 7 due to structural rearrangements (which thus has a different mechanism of origin as compared to monosomy, which is chromosome breakage vs non-disjunction) is frequently observed in association with mainly hematological disorders but a single common region of deletion has not yet been identified. Cytogenetics has made an enormous contribution to our understanding of the pathophysiology and prognosis of childhood leukemia **[**David G. Nathan, 2003**]**.

Children with AML generally show poor out come when their cytogenetic results represent monosomy 7 or monosomy 7 syndrome and different genetic disorders including Fanconi anemia, neurofibromatosis type 1, severe congential neutropenia and Schwachman –Diamond syndrome [Luna-Fineman et al, 1995 & Dabaja BS et al, 1999**]**. Sometimes CML patients that develop chromosome 7 abnormalities in Ph−ve cells, particularly monosomy 7, and they are appear to have the greatest risk of developing MDS/AML [Majd D. Jawad et al , 2016**]** After cytotoxic cancer therapy or occupational exposure to mutagens, patients with AML develop Monosomy 7 or deletions of 7q; but the significance of such abnormalities in childhood ALL is unknown [Marla J. F. O'Neill, 2012**].**

Materials and Methods

Conventional Cytogenetic, FISH and Clinical Details

Study of conventional cytogenetic using Giemsa Banding technique and Fluorescence in Situ Hybridization were carried out in hematologic malignant patients at cytogenetic laboratory of The Gujarat Cancer & Research Institute, Ahmedabad. Peripheral blood lymphocytes and Bone marrow sample was collected aseptically in Sodium Heparinized vaccuate. For conventional cytogenetic study, short term culture and GTG banding were carried out according to standard protocol **[**Deniz Tastemir et al 2011**]**. Well spreaded good morphology metaphases were captured in scanning and capturing system -Metafer(Zeiss-Germany) and analysis using IKAROS software and karyotype description was done using ISCN 2016 guidelines **[**McGowan-Jordan, J. ,Simons, A., Schmid, M 2016**].**

FISH probe LSI 7q D75486 7q13 in interphase and assay done using metaphase cells. The FISH probe LSI 7q D7S486 7q13 was labeled with: Orange signal for the 7q31 both loci and Green signal for the centromere of chromosome 7. 2O2G signal pattern indicating normal pair of chromosome 7 and 1O1G signal pattern indicating loss of a chromosome 7.

Table 1. *Clinical details of the patients*

Patient No.	Age/ Sex	Chief Complains	Spleenomegaly	Hb	White Blood Cell	Diagnosis	Treatment	Status
1	1/M	Cold, Fever, Cough,	-	9.4 gm/dl	84.2×10^3/ cmm	JMML	Hydroxyurea	Expired within 5 months
2	8/F	Fever, Gum bleeding, Rash all over	+	8.1 gm/dl	0.1×10^3/cmm	AML	Hydroxyurea	Expired within 1 month
3	9/M	Low grade fever	-	5 gm/dl	10.6×10^3/ cmm	AML-M4E0	Thioguinine	Expired within 6 months
4	10/F	Low grade fever, Weakness	-	7.4 gm/dl	2.47×10^3/ cmm	JMML	Hydroxyurea	Expired within 4 months
5	31/F	Nausea, Abdominal pain, Fever	+	7.5 gm/dl	60.9×10^3/ cmm	CML	Imatinib	Expired within 6 months

6	35/M	Lower limb swelling, Scrotal swelling, Low grade fever, Weakness	+	6.5 gm/dl	10.5×10^3/ cmm	CML	Hydroxyurea, Thioguinine	Expired within 1 month
7	35/M	Generalized weakness, shorten of breath	-	8.3 gm/dl	2.9×10^3/cmm cmm	AML	Thioguinine	Expired within 2 months
8	40/M	Low grade fever, Abdominal pain, Weakness	+	5.8 gm/dl	0.2×10^3/cmm cmm	AML	Thioguinine	Expired within 2 months
9	57/M	Weakness, Abdominal pain, Fever	+	4.7 gm/dl	0.2×10^3/cmm	AML	Hydroxyurea, Thioguinine	Expired within 2 months
10	53/M	Abdominal pain, fever	-	10.5gm/dl	$8.4X10^3$cmm	AML		Expired within 2months
11	60/M	fever, Weakness	+	8.7gm/d	$83.4X10^3$	CML-BC	Imatinib (400mg)	Alive
12	24/F	weakness, Shorten of breath, fever	+	7.4gm/dl	$199.8X10^3$	Chronic Myeloid Leukemia - Lymphoblastic crisis	Imatinib (400mg) Vincristin (1 mg)	Alive

Conventional Cytogenetic Data

In conventional cytogenetic study, G banded karyotype report showed 45 chromosomes with monosomy 7. Out of 12 patients 2 patients with CML diagnosis showed translocation 9 and 22 along with monosomy 7 whereas 2 CML patients showed sole monosomy 7 and 6 patients with AML and 2 with JMML showed sole monosomy 7 **(**Figure 1**)**. Conventional cytogenetic results using G banding described in Table 2.

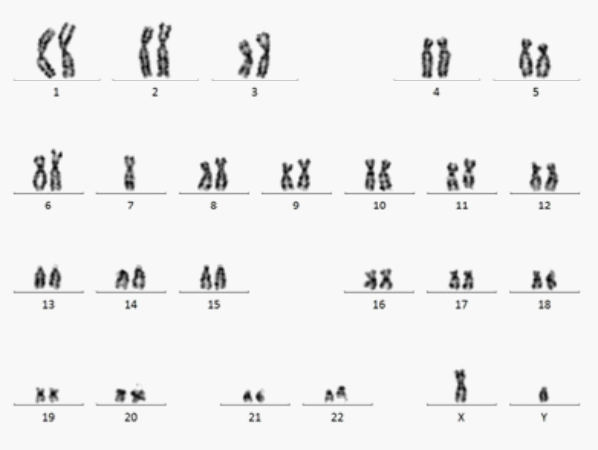

Fig 1. *Representative GTG-banded karyotype showed monosomy in all patients*

Table 2. *Conventional Cytogenetic results using G banding showing monosomy 7*

Sr. no.	Patient	Diagnosis	Conventional cytogenetics results
1	1/M	JMML	45,XY,-7[10]
2	8/F	AML	45,XX,(-7)[10]
3	9/M	AML	45,XY,(-7)[10]
4	10/F	JMML	45,XX,(-7)[15]
5	31/F	CML	45,XX,(-7),t(9;22)(q34;q11.2)[10]
6	35/M	CML	45,XY,(-7)[10]
7	35/M	AML	45,XY,(-7)[10]/46,XY[9]
8	40/M	AML	45,XY,(-7)[20]
9	57/M	AML	45,XY,(-7)[7]/46,XY[9]
10	60/M	CML-BC	45,XY,(-7),[18]/46,XY[2]
11	53/M	AML	45,XY,(-7)[20]
12	24/F	CML	45,XX,(-7),t(9;22)(q34;q11.2)[10]

FISH Results

In FISH study signal pattern OG considered as monosomy 7 with LSI 7q D7S486 7q13 probe. All patients showed OG pattern (Figure2).

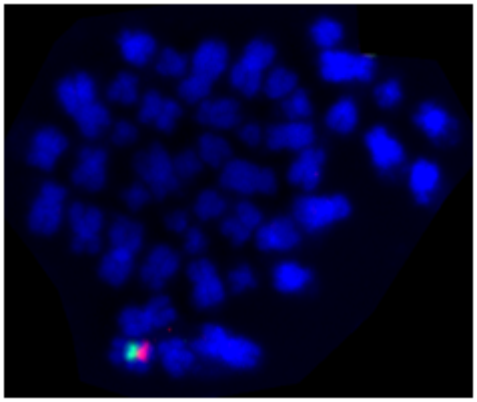

Fig 2. *FISH probe LSI 7q D7S486 7q13 is labeled with: Orange signal for the 7q31 both loci and Green signal for the centromere of chromosome 7. FISH signal pattern OG considered as monosomy 7.*

Discussion

Monosomy 7 is a disorder characterized by an extremely poor prognosis. It must be treated with stem cell transplantation. Even a matched unrelated donor transplant offers a better chance for survival than watchful waiting or chemotherapy. Monosomy 7 in pediatric patients associated with poor event-free survival when treated with conventional chemotherapy **[**AD Trobaugh-Lotrario et al, 2005**]**. Adults with monosomy 7 usually have multiple cytogenetic abnormalities, whereas the disorder is usually unadulterated in children. The haploinsufficiency associated with loss of the short arm of the chromosome is probably responsible for the development of malignancy that occurs at a variable rate even in patients with familial loss of the chromosome. The collection of monosomy 7 cells established by Kardos et al, 2003 provides an important opportunity to learn much more about this disorder. It is vital to study gene expression in monosomy 7 to learn how the chromosome disorder leads to malignancy. It is believed that loss of a key suppressor is responsible, but it is unclear whether this permits the uncontrolled expression of a tyrosine kinase that finally drives the leukemia **[**David G. Nathan, 2003**]**

Monosomy 7/del(7q) is frequent in secondary MDS or AML, and also in leukemias occurring in individuals with constitutional syndromes including predisposition to myeloid disorders; these findings suggest the presence of a putative myeloid leukemia suppressor gene in the commonly deleted genomic segment 7q22 and even multiple genes in 7q22 -31.1 that might be playing a role in leukemogenesis **[**Francois Desangles et al, 1999, Trivedi et al, 2011**]**. In our study, out of 12 patients with monosomy 7, our 11 patients expired with 1to 6 months of diagnosis and 1 patient with monosomy 7 is still alive and in remission.

In CML patients, during therapy with Imatinib Mesylate (IM), some patients develop chromosomal abnormalities in Philadelphia chromosome (Ph)-negative cells. These abnormalities are frequently transient and their clinical consequence is unclear. Although some reports have suggested that the abnormalities might be associated with secondary MDS, the diagnosis has not always been established using standard criteria [Kovitz C. et al, 2006]. Clonal cytogenetic abnormalities (CCA) were detected in Philadelphia chromosome (Ph)-negative cells in some patients with CML who attained a cytogenetic response to IM [Deininger M. et al, 2007] Monosomy 7 occurring in Ph cells can be a transient finding in CML patients on TKI treatment, and that it is not an absolute indication of the emergence of a new myeloid malignancy. In addition, while most cytogenetic abnormal, Ph myeloid clone have thus far been identified in CML patients treated with IM, with the increasing use of newer TKI such as Nilotinib, these Ph clones may be more commonly associated with the second generation of TKI. [Majd D. et al, 2016]. In present study 1 of the patient treated with Imatinib for CML and subsequently found to have sole monosomy 7 and Ph-negative cells in cytogenetic study and FISH with *BCR-ABL* also revealed that there was no fusion for *BCR-ABL*. Patient was expired within 2 months from diagnosis that indicates poor prognosis [Francois Guilhot 2016].

In accordance to Terezinha de Jesus Marques et al, 2008, Monosomy 7 is the most common cytogenetic abnormality among myeloid disorders during childhood, in our study there were 4 patients (40%) children. Monosomy 7 also occurs in some patients who are reported as having Juvenile Myelomonocytic Leukemia (JMML). Our 2 patients were having diagnosis of JMML. JMML has been described as an aggressive illness, with overall survival of approximately nine months. Patients often present repeated bacterial infections episodes, and most untreated patient die from organ failure due to infiltration of leukemic cells or infectious processes [Terezinha de et al, 2008, Guang Yang et al, 2017]

Children with Ph' ALL are known to respond poorly to intensive therapy but those with -7 in addition to the Ph' chromosome appear to fare even worse. New treatment strategies are needed for these children because this subgroup has a dismal prognosis. Bone marrow transplantation might be considered after initial induction of remission for patients with t(9;22) ALL with or without -7 [Carolyn Russo et al, 19991]. Monosomy 7, as a sole secondary abnormality, is also related with a poor prognosis and shorter survival in adult ALL cases [Walid AL-Achkar et al, 2014]. N A Heerema et al suggested that the critical region of loss of chromosome 7 that is associated with an inferior outcome in childhood ALL may be located on the p-arm. Russo et al suggested that a tumor suppressor gene on 7p might contribute to the poor outcome of children with ph+ve ALL and monosomy 7 or losses involving 7p. Our results are consistent with this hypothesis, and extend the significance of loss of 7p to Ph-negative childhood ALL. Thus although losses involving chromosome 7 are associated with a poor prognosis in both ALL and AML, the critical region of chromosome 7 may differ [N A Heerema et al, 2004]. The association of losses in 7q with myeloid leukemia suggests that this region contains a tumor suppressor gene or genes whose loss of function contributes to leukemic transformation or tumor progression. [Trivedi Pina et al, 2011].

Conclusion

The -7/del(7q) aberrations frequently coexist with complex karyotype such as -5/del(5q) and trisomy 8. Loss of chromosome material due to deletions of the long arm of chromosome 7, del(7q), is a consistent finding in all types of myeloid disorders, invariably associated with a poor prognosis. Two different segments, 7q22 and 7q32-q33, have been implicated as critical regions of gene loss associated with these disorders.

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Citation: **Pina Trivedi, Dharmesh Patel, Priya Varma, Dhara Ladani, Darshita Patel, Mahnaz Kazi, Prabhudas Patel.** *Assessment of Prognostic Significance of Monosomy 7 in Myeloid Malignancies Sole or with Recurrent Chromosomal Abnormalities: An Indian Experience. Archives of Hematology and Blood Diseases. 2018; 1(2): 08-14.*