RESEARCH ARTICLE

Outcomes of 1st Remission Induction Chemotherapy in Acute Myeloid Leukemia Cytogenetic Risk Groups

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Abstract

Background: Diagnostic karyotyping analysis is routinely used in acute myeloid leukemia (AML) clinics. Categorization of patients into risk stratified groups (favorable, intermediate and adverse) according to cytogenetic findings can serve as a valuable independent prognostic factor. **Method and Material:** A retrospective descriptive study was conducted based on the patient records of newly diagnosed non-M3 AML young adult cases undergoing standard 3+7 i.e, Daunorubicin and Ara-C (DA) as remission induction chemotherapy. Diagnostic cytogenetic analysis reports were analyzed to classify the patients into risk stratified groups according to South West Oncology Group criteria and prognostic significance was measured with reference to achievement of haematological remission after 1st induction chemotherapy. **Results:** A normal karyotype was commonly expressed, found in 47.2% of patients, while 65% (n=39) appeared to have intermediate risk cytogenetics, and 13.3% (n=8) adverse or unclassified findings. Favourable cytogenetics was least frequent in the patient cohort, accounting for only 8.3 % (n=5).The impact of cytogenetic risk groups on achievement of haematological remission was evaluated by applying Pearson Chi-square, and was found to be non-significant (df=12, p=0.256) but when the outcomes of favourable risk groups with intermediate, adverse and unclassified findings compared, results were highly significant (df=6, p=0.000) for each comparison. In patients of the favourable cytogenetic risk group, HR?? was reported in 40% (n=2/5), as compared to 62.2% (n=23/37) in the intermediate cytogenetic risk group, 57.1% (n=4/7) in the adverse cytogenetic risk group and 28.6% (n=2/7) in hte unclassified cytogenetic risk group. **Conclusion:** Cytogenetic risk stratification for AML cases following criteria provided by international guidelines did not produce conclusive results in our Pakistani patients. However, we cannot preclude an importance as the literature clearly supports the use of pretreatment karyotyping analysis as a significant predictive marker for clinical outcomes. The apparent differences between Pakistani and Western studies indicate an urgent need to develop risk stratification guidelines according to the specific cytogenetic makeup of South Asian populations.

Keywords: AML- haematological remission- remission induction chemotherapy- cytogenetics

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Introduction

Acute Myleoid Leukemia (AML) is a heterogeneous clonal malignancy (Hou et al., 2013; Su et al., 2013; Ahmed et al., 2014) which has been studied extensively in past few decades. Coming a step forward with the early French-American-British (FAB) classification (Bennet et al, 1985), World Health Organization (WHO) proposed the newer classification (Harris et al., 1999) which was revised in 2008 with the inclusion of prognostically significant cytogenetic and molecular markers (Vardiman et al., 2009). Therapeutic advancement in last three decades have led the clinicians to better understand the biology of disease as well impacts of some vital patient factors like age (Appelbaum et al., 2006) and genetics on the treatment outcomes (Foran, 2010).

Diagnostic karyotyping analysisis now routinely used in AML clinics (Döhner et al., 2010; O'Donnell et al., 2012; Estey, 2014). Categorization of patients into risk stratified groups (favorable, intermediate and adverse) according to the cytogenetics (Orozco and Appelbaum, 2012) can serve as a valuable independent prognostic factor (Haskell, 1995). Patients falling into these three risk groups respond differently to chemotherapy treatment in induction and post-induction phases of AML (Kottaridis et al., 2001) depending upon the specific cytogenetic or molecular marker they express (Slovak et al., 2000). So, the therapeutic paradigms are being shifting to develop and select the new target therapies and improvement of existing treatment strategies in cytogenetic subsets of adult patients.

Clinical trials by Medical Research Council (MRC), Cancer and Leukemia Group B (CALGB) and South West Oncology Group (SWOG) have categorized the patients into aforementioned three risk groups with some minor differences due to variation in patient selection and treatment strategies (Orozco and Appelbaum, 2012). Patients with complex cytogenetics express multiple

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unrelated cytogenetic abnormalities (Döhner et al., 2010). The SWOG and CALGB count it to be 3-5 and MRC classification needs it to be 4 or more to be labeled as complex (Orozco and Appelbaum, 2012).Complex cytogenetics, del (5q), abn (3q) and single or/and multiple monosomies are associated with potentially adverse outcomes and higher relapse rates with conventional treatment options in AML (Kumar, 2011). Monosomal karyotype can be commonly seen in AML patients (Breems et al., 2008). Favorable risk group patients have high rates of complete remission and overall survival following induction and consolidation therapy in AML (Byrd et al., 2002).Patients who express chromosomal aberrations like t (8;21), t (15;17), inv(16) or t (16;16) are categorized into favourable group (Slovak et al., 2000). Response to different chemotherapeutic agents can be predicted depending onthe individual expression of these aberrations in cytogenetic subsets (Patel et al., 2012) e.g. patients with inv (16) have better response with high dose regimens of Cytarabine (Byrd et al, 2002; Grimwade et al., 2010). Larger patient population fall into the intermediate risk group and these patient express normal cytogenetics (Shahab et al., 2015) or chromosomal aberrations +8, +6,-Y, del (12p). There is great heterogeneity in expected outcomes achieved by this group of patients in AML (Hou et al., 2013).

The findings by multiple extended trials have been translated to the globally accepted response predictive results of AML treatment in cytogenetic subsets. With standard induction therapy, young adults with favourable cytogenetic karyotyping achieve more than 80% complete remission rates with highest overall survival rates among all groups (Byrd et al., 2002). An intermediate risk group has remission rates between 65-75% with greater heterogenecity (Orcozo and Appelbaum, 2012). The un-favourable/adverse group has the dismal prognosis with less than 45% remission rates and least overall survival (Grimwade et al., 2010). In cases where combinations of complex cytogenetics with expression of some favourable translocations like t(8;2) or inv (16;16) can put positive weights in remission rates and overall survival as compared to the intermediate or adverse group (Orozco and Appelbaum, 2012).

Prospective trials on cytogenetics in South Asian populations are limited. In Pakistan the situation is even more dispiriting. Single-center studies have been published (Harani et al., 2006; Anwar et al., 2006; Aziz and Qureshi, 2008) but these can't represent the population cytogenetic patterns. Apart from inclusion of diagnostic cytogenetics in routine analysis, and practicing risk adaptive therapy approach, there is dire need of research trials in AML. In the present study, we categorized our patient cohort according to SWOG cytogenetic risk stratification and evaluated the remission rates after standard induction therapy 3+7(Daunorubicin and Ara-C).

Materials and Methods

Study Design and Data Retrieval

The present study is a descriptive, retrospective analysis done at National Institute of Blood Disease and Bone Marrow Transplantation. We evaluated the diagnostic cytogenetic analysis reports of 72 patients out of which 12 patients were excluded due to the reasons of clotted samples, low yield or financial constraints.

Patients Cohort

Inclusion Criterion

Young adults aged between 15-60 years with morphologically documented diagnosis of previously untreated de novo non-M3AML had been included in the study. Peripheral blood or bone marrow samples were taken at the time of presentation for cytogenetic analysis.

Exclusion Criterion

We excluded all patients of age below 15 years, and those who had transformed AML or patients who had been given with supportive therapy with low dose Cytarabine.

Chemotherapy Administration

Following MRC trial 2004, all patients were administered 3+7 i.e., Daunorubicin and Ara-C (DA) chemotherapy as standard induction therapy. Cytarabine (also known as Ara-C) in the dose of 100mg/m2 from day 1 to day7 and Daunorubicin in the dose of 50mg/m2 on day 1, 3 and 5 was administered to the patients.

Study Parameters

Patients' cytogenetics analysis (Banded Chromosome Analysis) was done on microscope using peripheral blood or bone marrow samples. 20 metaphase cells were analyzed to establish the diagnosis of a normal karyotype and abnormal karyotype from bone marrow. On the basis of results, patients were classified into different groups of risk stratification according to South West Oncology Group (SWOG) (Slovak et al., 2000) as mentioned in Table 1.

The primary end point of the study was to evaluate the remission rates achieved by patients in different risk groups after 1st induction therapy. Haemtaological Remission (HR)was documented as per following criterion (Cheson et al., 1990, 2003; Döhner et al., 2010).

→ *Bone marrow blasts less than 5%*
→ *Absence of extramedullary disease*
→ *Absolute neutrophil count ≥1.0 × 109/L (1,000/μL)*
→ *Platelet count ≥ 100 ×109/L (100,000/μL)*

Induction failure was documented as,

→ *Bone marrow blasts >5%*
→ *Reappearance of blasts in the blood*
→ *Development of extramedullary disease or persistent leukemia*

Death was documented as,

→ *Death occurring fewer than 7 days after completion of first induction is early death*
→ *Death occurring more than 7 days after completion of first induction with no blast in blood but no bone marrow available is death from intermediate cause.*

Statistical Analysis

We analyzed the data by Statistical Package for Social

Table 1. Cytogenetic Analysis Results

Cytogenetics	No. of Patient (n=60)	% Patient
Favorable	5	8.3
Intermediate	39	65.0
Adverse	8	13.3
Unclassified	8	13.3

Sciences (SPSS) version 20. Pearson Chi-square test wasapplied for evaluation of significance of variables within the group. The values $p<0.05$ are considered to be significant, $p<0.001$ as more significant and $p< 0.0001$ as highly significant.

Results

As we included only the young adult patients, the median age at the time of presentation is reported to be 32 years in our cohort. The majority of the patients were male (n=42) with male: female ratio of 2.3:1.Normal karyotype was the most commonly expressed and 34 (47.2%) patients were carrying it. Cytogenetic analysis report revealed that 65% (n=39) patients appear to have intermediate risk cytogenetics, 13.3% (n=8) have adverse cytogenetics. Favourable cytogenetics is least to appear in patient cohort with 8.3 % (n=5). 8 patients fall into unclassified cytogenetic risk group (Table 2). Cytogenetic aberration t (8;21) and complex cytogenetics have relatively higher but statistically insignificant prevalence rates.

The impact of cytogenetic risk groups on achievement of haematological remission was evaluated by applying Pearson Chi-square, and consequent results show that there is insignificant association (df=12, p=0.256) between cytogenetic risk groups and achievement of HR. The overall remission rate is 55.3% (n=31/56) with 44.6% (n=25/56) induction failure. In 4 patients the bone marrow response could not be evaluated due to early death/death from intermediate cause and we excluded these patients to minimize the variability in the results.

In patients with favourable cytogenetic risk group, HR is reported to be 40% (n=2/5), with intermediate cytogenetic risk group, HR is reported to be 62.2 % (n=23/37) .In patients with adverse cytogenetic risk group, HR is reported to be 57.1 % (n=4/7) and with unclassified cytogenetic risk group, HR is reported to be 28.6% (n=2/7). These results are shown in Table 2.

The rate of early death/death from intermediate cause is equal (12.5%) in adverse and unclassified risk group (n=1/8). No death is reported in favourable group and intermediate risk group has low death rate (5.1%, n=2/39).

To further validate the results, we again applied Pearson Chi-square to find out the association of achievement of HR among different cytogenetic risk groups, and compared the outcomes of favourable risk group with those of intermediate, adverse and unclassified. The results

Table 2. Haematological Remission in Cytogenetic Risk Group [4 Patients were Excluded due to Early Death/Death from Intermediate Cause]

Risk Groups	No.(%) of Patients achieving HR
Favourable	
46, XX, t(8;21)(q22;q22)(14)/46,XX,(01),	
47, XX, +4, t(8;21)(q22) (q22){09},	40.0%
47 XY, +4t(8:21)(Q24:Q22)11/46,	(n=2/5)
XY, t(8:21)(q24:q22)(12)/46, XY(05),	
45XY, t(8;21)(q22;q22)-20(12),	
46, XY, t (8;21) (q22;22) [15]	
Intermediate	
Normal male/female, del 9q, trisomy 21, 46, XY, t(6;11)(q27;q23)(17)/46XY(03),	62.2%
46, XX, t(9;11)(q23;q230[15], 46, XY, - 8, +12 [15]	(n=23/37)
Adverse	
Complex,46,XY,t(9:22)(q34;q11.2)(15),	
46, XY, t(10;11) (q22:q25), del (15) del (?q11.2q15)[20}, 45 XY, del 3(q26;1), -7,+mar(15),	57.1%
Complex, 46 XY, t(8;19) (q22;13), inv (9) (p12q13) (28)/46 XY (04),	(n=4/7)
45, X, -Y [2]/46, XY [18]	
Unclassified	
47,XX,+15(12),	
47, XY, +19(15),	28.6%
45,XX,add 7(q32), -16(15),	(n=2/7)
85~89 Hyperploidy (21)/46, XY (04),	
Hyperploidy(15)/46 XX (1C)+3+8+9+14,	
34~45 Hypodiploidy[13]/93~103 Hypertetraploidy [4]/46, XY(20)	
47, XX, +4(19)/46, XX(01)	

Table 3. Comparison of Outcomes of Favourable Group with Adverse, Intermediate and Unclassified

Comparison	Death	Failure	HR	P value
Favorable Vs Adverse				
Adverse (n=8)	1	3	4	0.000
Favorable(n=5)	0	3	2	
Favorable Vs Intermediate				
Intermediate(n=39)	2	14	23	0.000
Favorable(n=5)	0	3	2	
Favorable Vs Unclassified				
Unclassified (n=8)	1	5	2	0.000
Favorable(n=5)	0	3	2	

Data is analyzed by Peasrson Chi-square p<0.0001 = highly significant

we obtained are highly significant (df=6, p=0.000) for each comparison (Table 3). In this comparison, we also included the patients who had reported death.

Discussion

From long time clinicians have been using clinico-pathological and haematological features for not only diagnosis of acute leukemias but to count for prognostic values too. Even at present we can not negate the importance of the clinical findings at the time of presentation but the discrimination of the patients into the risk stratified groups according to their cytogenetic profiles has proven to be of the utmost prognostic significance.

The present study in Pakistani patients, aims to distinguish the AML patient subsets by diagnostic karyotyping analysis who can better respond to the conventional treatment. The previous studies on cytogenetics in Pakistan have mostly aimed for descriptive analysis and mostly researchers did not focus on the treatment outcomes (Anwer et al., 2006; Aziz and Qureshi, 2008). Yet there are few researches with same objective as ours (Harani et al., 2006) who have presented their study results which can be referred for the comparison to present study outcomes but to some extent these are considered compromised because of variable or small sample size and due to variation in treatment. Our selection of young adults limits the variation in results as found in other studies by selecting all age groups. We also excluded the M3 subtype and those patients who had received low dose chemotherapy so the variation of the treatment can be minimal. However the limitation of the study is that it was a single center experience and a retrospective analysis.

As like most local studies, (Harani et al., 2006; Aziz and Qureshi, 2008; Naseem et al., 2013; Sultan et al., 2016) AML prevalence in males is found ascended in our cohort. The male to femaleratio, 2.3:1 is close to Aziz and Qureshiand Naseem et al who have reported it to be 2:1 and 3:1 respectively. However mostly studies have report this ratio around 1.3-1.6:1 in Pakistan. AML in Pakistan is reported in comparatively much younger ages i.e., at late 30s as Sultan et alreports the median age 34.5 and Kakepoto et al as 38 as compared to the West where median age is reported to be 67 years (NCI, 2014). Increasing age has been considered a bad prognostic indicator in AML and we found that those patients aged between 31-55 years have lower remission rates than patients below 30 years of age.

The clinical presentation at the time of diagnosis was well in accordance to the findings of local studies (Fozia and Aziz, 2008; Asif and Hasan, 2013; Shahab and Raziq, 2014; Sultan et al., 2016). Majority of the patients had common early signs like fever, pallor, anemia and weakness with Eastern Cooperative Oncology Group (ECOG) (Oken et al., 1982) performance status 2 and 1.

Cytogenetical analysis reports show that most of the patients express normal karyotype. This feature combined with other cytogenetic abnormalities leads to inclusion of majority patients in the intermediate risk group likewise reported by Harani et al. The overall remission rate in our study is 55.3% which is comparatively lower than the West (Estey and Döhner, 2006; Erba, 2010). The association of achieving HR among different cytogenetic groups is found to be insignificant with p=0.256. This means that despite the extensive data published in support to use diagnostic cytogenetics as an important prognostic tool (Haskell, 1995; Slovak et al., 2000; Byrd et al., 2002), the results in Pakistani AML patients show a different picture. As we had limited number of patients and followed the cytogenetic risk stratification criterion which was produced by research on American patient population, there could be some genetic and geographical differences between them and Pakistani population which probably have compromised the overall results. On the other hand, highly significant results obtained in the comparison of favourable group with intermediate, adverse and unclassified (with inclusion of death toll in each group) enlighten the clinical usefulness of cytogenetic risk stratification in our study. As we obtained very low remission rate in the favourable group even less than the adverse risk group, so to uncoil the intricacy of this scenario, we chose to compare the outcomes of favourable risk group with those of adverse, intermediate and unclassified risk groups and found significant correlation. But here, impact of inclusion of death toll in each group is important. As there was no death reported in favourable group, lower rate in intermediate and highest rate in adverse risk group, this impact probably has contributed significantly in the comparison of within groups association.

The most unanticipated result we have obtained in the study is markedly low HR rate in favourable group i.e 40%, which is neither close to local or international studies. Most studies refer the favourable group with more than 80% remission rates in well-controlled trials (Byrd et al., 2002; Grimwade et al., 2010; Orozco and Appelbaum, 2012). Pakistani study Harani et al reports it be 100% but the very small sample size (n=3) undermines the significance of this result. On the other hand, our intermediate risk group has comparatively higher results than a study by Harani et al., (2006) on Pakistani AML patients but lower remission rates than reported by Byrd et al., (2002) in American AML patients. Similarly our adverse and unclassified groups have reportedly higher

remission rates than Harani et al., (2006).

A striking observation in the present study is that there is no death reported in favorable group which is agreeable with the published data. On the contrary, death rate is low in intermediate risk group. Adverse risk group and unclassified group have reported equal frequency of deaths. This trend along with other results shows that patients expressing chromosomal aberrations in unclassified group have poor remission rates and can be classified to adverse group based on the high induction failure and death rates. Another reason may be the sample size variation within the groups. We accept that the sampling distribution among different groups is uneven which could be a reason of deviant and unusual findings in comparison to other studies.

The reasons for these unprecedented results could be different genetic makeup of Pakistani patients and the incapability to include some genetic aberrations in favorable, intermediate and adverse group, consequently designated as unclassified. Other possible reasons shall be pondered upon too. Nevertheless, we can improve the results in favourable and intermediate group by interventions in chemotherapy dosing. Daunorubicin in higher dose (90 mg/m^2) combined with standard dose Cytarabine results in better remission rates and prolonged overall survival than conventional dose of (50mg/m^2).This trend is also observed in adverse risk group but to a lesser extent (Fernandez et al., 2009; Orozco and Appelbaum 2012).Research on genetics in Pakistan is confined to very few institutes and scarce published data limits the possibilities to compare the results with the similar study objectives in our patient population.

Cytogenetic risk stratification in AML following criteria given by international guidelines could not produce conclusive results in Pakistani patients. However, we can't deny its importance as the literature evidently supports the use of pretreatment karyotyping analysis as a significant predictive marker for clinical outcomes in AML. The differences in results between Pakistani and Western countries studies indicate the urgent need to develop risk stratification guideline according to the cytogenetic makeup of South Asian populations. Establishing a multicentre cancer network should be considered which can set up extended and well controlled clinical trials in the field of genetics and therapeutics and accordingly propose guidelines for the management of haematological malignancies. Possible therapeutic interventions like dose intensification or modification according to the integrated cytogenetic analysis can tend the clinical outcomes in ascending direction.

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