Original Article

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Response to Induction Chemotherapy Predicts Survival in AML: A Single Centre Experience from North India

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Abstract

Aim: The present study was carried out to analyze the various patient related (e.g. age, sex, performance status), disease related (white blood cell count, cytogenetic and molecular mutational status)and treatment related (delay in treatment initiation and response to induction chemotherapy)variables as predictors of outcome in acute myeloid leukemia (AML) patients presenting to a tertiary care center in North India. *Materials and Methods:* Thedata of all newly diagnosed *de-novo* AML patients who presented to our center from January 2015 to December 2017 and opted for chemotherapy was correlated with treatment outcome. *Results:* Sixty eight patients underwent induction chemotherapy during the study period. Sixteen (23.5%), 49 (72.1%) and 3 (4.4%) were in the favorable, intermediate and adverse risk groups, respectively. Fifteen (22%), 8 (11.7%) and 11 (16.1%) patients were positive for AML-ETO, NPM1, FLT3 mutations (3 patients had FLT3 D835 mutations), respectively. Exon 17 c-kit mutations were seen in 10 (14.7%) patients. We did not observe any exon 8 c-kit mutations in our cohort of patients. Biallelic CEBPA mutations were seen in 6 patients (8.8%). Following induction chemotherapy, 26 (38.2%) patients attained complete remission (CR), 20 (29.4%) achieved incomplete CR (platelet count<100 x 10^9/L) and 22 (32.4%) were refractory to induction therapy. There were only 3 (4.4%) induction deaths.High TLC was associated with FLT3 mutations (p=0.03) and presence of extra medullary disease correlated with AML-ETO (p=0.02) and c-KIT mutations (p=0.02). There was statistically significant correlation of FLT3-ITD mutation positive patients with risk of relapse (p= 0.001). The 2 yr Overall survival (OS) and Event free survival (EFS) were 39.6% and 22.8%, respectively. In a multivariate analysis, the performance status (PS) and post induction remission status independently predicted survival. *Conclusion:* Thus our data highlights that PS and post induction remission status translates into better OS.

Keywords: Acute Myeloid Leukemia; Induction Chemotherapy; Molecular Mutations; Prognosis, Survival.

Introduction

Acute Myeloid Leukemia (AML) is a clonal malignant disorder arising from hematopoietic stem/progenitor cells characterized by myeloid differentiation arrest or abnormal proliferation. It accounts for approximately 20% of acute leukemia in children and 80% of acute leukemia in adults. The overall age adjusted incidence rate is reported to be 4.0 cases per 100,000 persons and the incidence increases with advancing age (>65 years) [1].

Traditionally conventional cytogenetics had been used to risk stratify AML patients into: Favorable (Core Binding Factor leukemia: t (8; 21); inv 16); Intermediate (Normal Karyotype) and Adverse groups (Complex karyotype, monosomy 5, monosomy 7). The novel molecular mutations recently been shown helpful in redefining prognostic subgroups in AML are: c-KIT; Nucleophosmin1 (NPM1); FMS-like tyrosine kinase (FLT3)-ITD (Internal Tandem Duplication); CCAAT/enhancer-binding protein (CEBPA) [2,3]. The characterization of the gene mutations has provided insights into the mechanisms of leukemogenesis and these gene

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mutations have emerged as important prognostic and predictive markers. Novel therapies are now being developed that target these molecular changes. Similar to Acute Lymphoblastic Leukemia (ALL), response to induction chemotherapy is also now emerging as an independent predictor of relapse in AML patients. Minimal Residual Disease (MRD) status and type of response (CR v CRp or CRi) play an important and perhaps dominant role in planning post induction therapy. Chen *et al* demonstrated that MRD status at the end of induction was the strongest predictor of relapse in newly diagnosed de novo AML (Hazard ratio (95%CI): 3.28 (1.87-5.75) [4].

Hence, in this prospective study, the aim was to study the impact of various disease, patient and treatment related factors on overall survival (OS) in newly diagnosed *de novo* AML patients presenting to a tertiary care center in North India.

Material and Methods

Patients and Treatment

This study was a prospective observational study that included 68 consecutive *de novo* AML patients between 2-60 years of age, who received induction chemotherapy at the Department of Hematology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, between January 2015 and December 2017.

All newly diagnosed AML cases (according to WHO 2016 Criteria**)** [5] who were eligible for receiving standard dose induction regimens i.e. 7+3 (cytosine arabinoside 100mg/m2/day x 7 days by continuous intravenous infusion and daunomycin 60mg/m2/day x 3 days) or Cytarabine plus Idarubicin plus etoposide (BFM-2004 protocol)for patients ≤ 18 yrs were included in the study [6]. In patients who were not in remission after 3+7 induction, second induction with HAM (high dose cytosine arabinoside 3 g/m2 /dose q 12 h on days 1, 3 and 5 with Mitoxantrone 12 mg/m2 /day on day 2, 4 and 6) was administered. Relapsed AML, therapy related AML, Acute Promyelocytic Leukemia and cases with prior therapy with hypomethylating agents (Azacytadine & Decitabine) were excluded. Individual patient proformas were filled to collect the essential clinical, laboratory and follow up data. Bone marrow and peripheral blood samples (5 ml each) were collected from the patients at the time of diagnosis after getting the written informed consent. The leukemia subtypes were established according to the FAB classification and the diagnosis was pathologically confirmed. All the patients who received induction chemotherapy were categorized into 3 risk groups based on cytogenetics and molecular mutations viz: favourable, intermediate and unfavourable [2]. Patients in remission after induction phase were given 4 cycles of consolidation chemotherapy with high dose cytarabine (3 g/m2 /dose q 12 h on day 1, 3 and 5). Induction chemotherapy was labelled as abbreviated if any patient received less than standard dose 3+7 (daunorubicin + cytarabine) chemotherapy. In patients who received abbreviated induction chemotherapy (either due to poor PS or severe sepsis at diagnosis) and did not achieve CR on response assessment were subjected to re-induction chemotherapy and the response post re-induction was used for all further statistical analysis. Febrile neutropenia was managed as per institutional protocol. After completion of therapy, patients were in follow up on a monthly basis. Response definition was according to the criteria proposed by the International Working Group [7]. CR was defined as <5% blasts by morphologic evaluation (based on 200-cell count), neutrophil count ≥ 1,000/µl and platelet count ≥ 100,000/µl. Criteria for CRp wereidentical but with a platelet count < 100,000/µl. CRi was said to be present if morphologic blast count was <5% and absolute neutrophil count <1,000/µl. However, in this study, the subgroups CRi and CRp have been clubbed together as incomplete CR (iCR) for all further statistical analysis.

Informed consent was obtained for all individuals participating in this study. All procedures performed in this study were in accordance with the ethical standards of the institution and with the 1964 Helsinki's Declaration

Immunophenotyping

Flow cytometry was performed on PB/BM on a six-color flow cytometer (FACS Canto II [Becton Dickinson, San Jose, CA, USA] using standard protocol. Monoclonal antibodies used in this study included fluorescein isothiocyanate, phycoerythrin, or peridinin chlorophyll protein, allophycocyanin labeled CD45, CD2, CD3, CD4, CD5, CD7, CD10, CD13, CD14, CD19, CD22, CD33, CD34, CD38, CD56, CD117, human leukocyte antigen D related (HLA-DR), and isotype control IgGs.

Molecular Analysis

DNA Extraction: Done by using PureLink genomic DNA mini Kit (invitrogen) and after extraction quality and quantity of DNA was checked by nano-

biophotometer. DNA with a quality ratio (260/280) between 1.7 to 2.0 was used for the study.

Total RNA Extraction: Done by using PureLink RNA mini Kit (invitrogen) and after extraction quality and quantity of DNA was checked by nano-biophotometer. RNA with a quality ratio (260/280) between 1.7 to 2.0 was used for the study.

FLT3-ITD & NPM1 Mutation Detection: A multiplex PCR amplification of genomic DNA using fluorescent-labeled primers to exon 14 and exon 15 of FLT3 yield a 310 bp fragment from wild type allele, and primers to exon 12 of NPM1 yield a 169bp fragment from wild type (WT) alleles. Fragment analysis of PCR products was done by genetic analyzer for the presence of internal tandem duplication in FLT3 gene and an insertion of 4 bp in nucleoplasmin 1 gene for the presence of mutation in these genes. Data was analyzed using Gene Mapper software V5.0 (Applied Biosystems, USA).

C-kit Mutation Detection in Exon 17 (Point Mutations): After PCR, band of target gene was analyzed over 2.0% agarose gel and purification of target gene band was done using Gel extraction kit (Genetix-Brand). Point mutations were identified using direct sequencing of PCR products using Big Dye v 3.1 (Applied Biosystems, USA) sequencing reaction kit. The sequencing was performed on ABI 3500 Genetic analyzer (Applied Biosystems, USA), and the sequences were analyzed using variant reporter software V3.0 (Applied Biosystems, USA) with reference sequence alignment.

C-kit Mutation Detection in Exon 8 (Insertions/ Deletions): PCR with labeled primers used to amplify a 219 bp products followed by capillary electrophoresis and fragment analysis for check insertion and deletions in exon 8. Data was analyzed using Gene Mapper software V5.0 (Applied Biosystems, USA).

CEBPA Mutation Detection: To detectmutationin human *CEBPA* gene, whole human *CEBPA* DNA (100ng) was amplified by four different primers set followed by direct sequencing of these PCR products using Big Dye v 3.1 (Applied Biosystems, USA) sequencing reaction kit, where each of the amplification primer was used at a concentration of 1pmol to read complete human *CEBPA* gene from both forward and reverse side. The sequencing was performed on ABI 3500 Genetic analyzer (Applied Biosystems, USA), and the sequences were analyzed using variant reporter software v3.0 (Applied Biosystems, USA) with reference sequence alignment.

Statistical Analysis

Descriptive statistics were obtained using mean with standard deviation or median with range and categorical variables were represented by frequencies with corresponding percentages. Differences in the distribution of individual parameters among subsets of patients were analyzed using Fisher exact test or the chi square test for categorical variables and the Mann-Whitney U test for continuous variables. Overall survival (OS) was defined as date of diagnosis to date of death or date of last follow up for those censored. Event free survival (EFS) was calculated from date of initiation of treatment to date of relapse, death or last follow-up. Survival curves for OS & PFS were drawn employing Kaplan-Meier method and were compared using log rank test. Cox proportional hazard regression model was applied to consider each potential prognostic factor in univariate and multivariate analysis. Adjusted hazard ratios (HRs) were estimated with 95% confidence intervals.Cox proportional hazards regression model was used to evaluate the risk factors for OS. Potential prognostic factors tested for the univariate analysis comprised of age, sex, performance status (PS), white blood cell count, percentage of blasts in bone marrow, cytogenetic risk group, type of chemotherapy, delay in treatment initiation, intercycle delay, mutational status, post induction remission status etc. Variables with p-values of <0.05 in the univariate analysis were included in the final multivariate model. Statistical analysis was done using SPSS Version 20.0 (SPSS Inc., Chicago, IL, USA) software.

Results

Patient Accrual and Baseline Characteristics

Over the period of this study there were 235 newly diagnosed cases of AML, of which only 68 (24.7%) received treatment at our center, and were thus included in the study. Males constituted 54.4% of total cases. Twenty- three patients (33.8%) were between 2-10 years, 27 (39.7%) were between 10 and <40 years and 18 (26.5%) were between 40 and <60 years old. The median age of the patients was 30 years (range: 3-59 years). The baseline demographic characteristics of newly diagnosed patients with AML receiving induction chemotherapy at our center are summarized in Table 1.

Table 1: Baseline Characteristics of AML patients

Parameter	N (Range/%)
Male (n)	37(54.4%)
Median age (years)	30 (3-59)
Pediatric patients (<18 years of age) (%)	18(26.4%)
PS (ECOG) n (%)	
1	41(60.3%)
2	21(30.9%)
3	6(8.8%)
Median WBC (x 10^9/L)	14.1 (0.3-313.9)
Median BM blasts (%)	77.5%(35-90)
Post induction marrow remission (%)	46 (67.6%)
Deaths during induction (%)	3(1 pediatric, 2 adults) (4.4%)
Induction failures/ refractory ds (%)	22(32.4%)
Median time from diagnosis to chemotherapy (days) (%)	50 (33-73)
Type of induction therapy, n (%)	
Full	48(70.5%)
Abbreviated	20(29.5%)
3+4	14
2+5	6

Table 2: Cytogenetics & Molecular mutation profile of AML patients

Karyotype	N (%)
Favourable	16(23.5%)
t(8,21)	13
Inv 16	3
Intermediate	49(72.1%)
46 XX/XY	44
+21	1
+22	1
T(3,5)	1
+8	1
Dup(18)	1
Unfavourable (complex karyotype)	3(4.4%)
Complex karyotype	1
T(5,11)	1
Inv 3	1
Mutation	**N (%)**
CBF (AML-ETO)	15(22%)
NPM1	8(11.7%)
FLT3-ITD	11(3 D835+) (16.1%)
CEBPA (Biallelic)	6 (8.8%)
c- kit (exon 8)	Nil
c-kit (exon 17)	10 (14.7%) K93N- 7/10 F89L- 5/10 S92P- 5/10 A91Q fs- 4/10 N94S- 2/10 R137G- 2/10 D123V- 1/10 L138P- 1/10 P139I- 1/10

Cytogenetics and Molecular Data

Cytogenetics data was available in all 68 patients and of these, 16 (23.5%), 49 (72.1%) and 3 (4.4%) were in the favorable, intermediate and adverse risk groups respectively. The various molecular mutations in our cohort of patients were as follows: 15 (22%), 8 (11.7%) and 11 (16.1%) were positive for AML-ETO, NPM1, FLT3 mutations (11 patients had FLT3 ITD mutations and 3 patients had FLT3

D835 mutations) respectively. Biallelic CEBPA mutations were seen in 6 patients (8.8%). Exon 17 c-kit mutations were seen in 10 (14.7%) patients. Of these 10, 5 (50%) were associated with core binding factor mutations (AML-ETO positive) and 1 patient had FLT3-ITD mutation also. The various mutations seen are summarized in Table 2.

Response to Induction Chemotherapy

The median time to start chemotherapy from diagnosis was 50 days (Range- 33- 73 days). 80% patients had a treatment delay of > 4 weeks after diagnosis. Out of the 68 patients who received induction chemotherapy only 48 (70.5%) patients could receive full chemotherapy whereas in 20 patients (29.5%), chemotherapy had to be abbreviated ('3+4' in 14 and '2+5' in 6 patients), as they developed high grade fever (>101 degrees Fahrenheit) along with features of severe sepsis such ashypotension, organ dysfunction etc. After induction chemotherapy, 26 (38.2%) patients attained complete remission (CR), 20 (29.4%) achieved incomplete CR and 22 (32.4%) were refractory to induction therapy. Of the 22 patients who were refractory to induction chemotherapy 14 (63.6%) patients received abbreviated chemotherapy (Figure 1).

Induction Deaths

Of the 68 patients in whom induction chemotherapy was initiated there were only 3 (4.4%) induction deaths. These included one pediatric and 2 adult patient. The cause of death in 2 patients was bacterial sepsis (due to multi-drug resistant bacteria- *Stenotrophomonas maltophila, Klebsiella pneumonia*) and in 1 patient due to fungal infection. The median time to induction death was 22 days (range: 15–32 days).

Post Induction Therapy Follow-Up

Out of the 22 patients who had induction failure, 11 (50%) received 2nd induction therapy of which 4 (36.4%) achieved remission. Of the rest 11 patients, 03 patients died during induction (Induction deaths), 08 patients opted for only supportive care due to lack of finances for continuing treatment.

Amongst patients with delayed therapy > 4 weeks, 22 (32.8%) patients had a disease relapse during a median follow up period of 16 months. Three patients underwent allogeneic stem cell transplantation in first CR (all were FLT3-ITD positive). The detailed analysis of patient's outcome is shown in Figure 1.

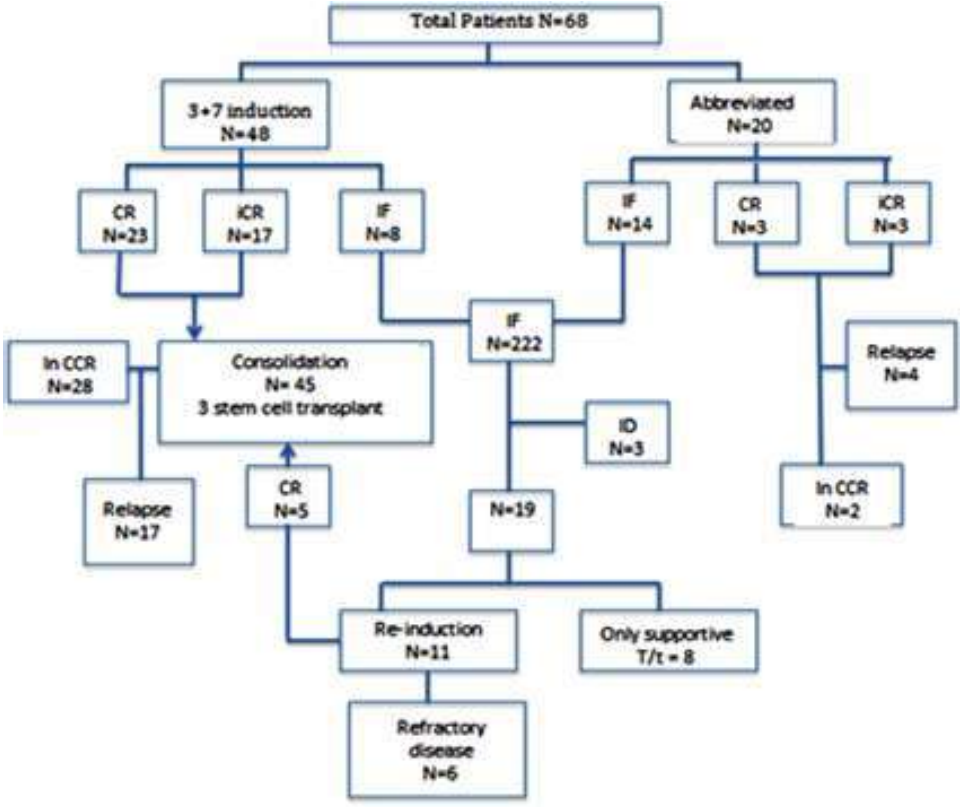
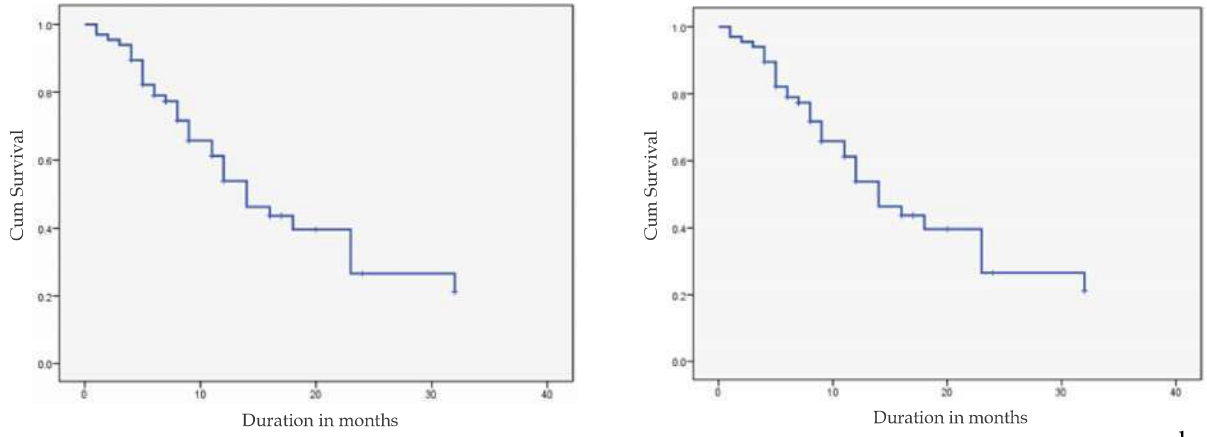


Fig. 1: Flowchart showing treatment given, response and follow up. CR-Complete remission, iCR – Incomplete remission, ID- Induction death, IF- induction failure, CCR-continuous complete remission

Survival

There were total 38 events (21 relapses, 03 induction deaths, 8 patients defaulted treatment and were lost to follow up and 6 had refractory disease) with a median follow up of 9 months (Range, 1-32 months). 30 (44.1%) patients continue to be in complete remission at the last follow up date. The 2 yr OS was 39.6% with a median OS duration of 14 months (95% CI - 9.95 - 18.04 months) (Figure 2b). The 2 yr EFS was 22.8% with a median EFS duration of 12months (95% CI - 6.35 - 17.64 months) (Figure 2a). According to remission status, the 2 yr OS amongst patients with CR, incomplete CR and no CR were 49.2%, 20.2% and 0% respectively (p= 0.001) (Figure 3). We did not observe any statistically significant difference in OS among patients with respect to presence or absence of molecular mutations. However, a statistically significant difference in EFS was demonstrated in patients with FLT3-ITD positive mutations (Table 3). There was also no statistically significant difference in OS between pediatric and adult patients (p=0.23).



a b

Fig. 2: a) Event free survival and b) Overall survival of AML patients

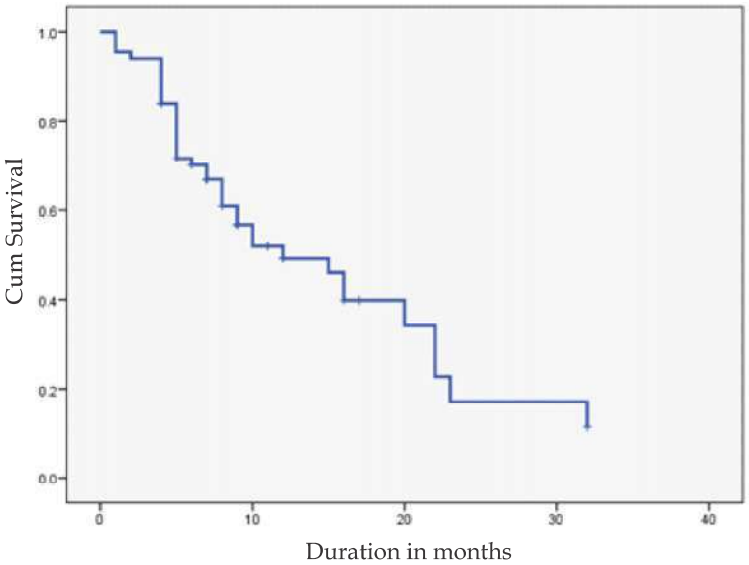


Fig. 3: Overall Survival according to remission status post induction

Table 3: Overall Survival (OS) & Event Free survival (EFS) stratified according to molecular mutations in AML

Molecular mutation	2 yr OS (Positive vs Negative)	p value	2 yr EFS (Positive vs Negative)	P value
FLT3-ITD	18.7% vs 28.2%	0.593	0% vs 21.9%	0.02
NPM1	30% vs 25.1%	0.714	46.9% vs 40.6%	0.514
Biallelic CEBPA	62.5% vs 23.7%	0.485	33.3% vs 17.5%	0.957
c-KIT (Exon -17)	18.5% vs 32.8%	0.972	16% vs 18.6%	0.414

Prognostic Factors

The analysis of associations of molecular mutations was done with various pre and post treatment variables. High TLC was associated with FLT3 mutations (p=0.03) and presence of extra medullary disease correlated with AML-ETO (p=0.02) and c-KIT mutations (p=0.02). There was statistically significant correlation of FLT3-ITD mutation positive patients with risk of relapse (9 out of 11 patients relapsed) (Table 4). Several clinical, biological and treatment-related data were correlated with achievement of post induction remission status, OS and EFS. A performance status less than 2 was found to be a significant factor on binary logistic regression analysis

Table 4: Analysis of association of molecular mutations with pre and post treatment parameters (p values)

Pre treatment variables	AML-ETO	NPM1	FLT3	CEBPA	c-KIT
Age	0.34	0.54	0.16	0.32	0.53
Sex	0.57	0.62	0.71	0.88	0.79
TLC	0.5	0.35	0.03	0.55	0.7
Platelet count	0.295	0.61	0.24	0.62	0.44
Blast% in BM	0.67	0.83	0.06	0.64	0.42
Extramedullary disease	0.02	0.3	0.15	0.24	0.02
Post treatment variables					
Death	0.178	0.31	0.123	0.69	0.559
Relapse	0.83	0.64	0.001	0.38	0.402
Post induction Remission	0.06	0.51	0.889	0.67	0.901

Table 5: Results of univariate and multivariate analyses to identify prognostic variables for overall survival (n=-68)

Univariate Analysis

Factor	Number	HR	CI	P value
Age				
<18 years	18		0.444-2.341	0.963
≥18 years	50	1.02		
Sex				
Male	37		0.429-1.952	0.818
Female	31	0.915		
PS				
<2	41		1.756-10.921	0.002
≥2	27	4.379		
Chemotherapy				
Full	48		0.634-3.904	0.329
Abbreviated	20	1.573		
TLC				
<50	50		0.382-2.148	0.823
≥50	18	0.906		
LDH				
<500	16	1.975	0.59-6.606	0.269
≥500	52			
Blasts				
<50%	14	1.139	0.426-3.042	0.795
≥50%	54			
Delay in treatment				
<30 days	14	1.411	0.555-3.587	0.469
>30 days	54			
Post induction remission				
CR	26+20	0.153	0.066-0.366	0.001
NoCR	22			
Mean intercycle delay				
<30 days	26	2.775	1.225-6.287	0.014
≥30days	42			
Type of cytogenetics				
Good	16			
Intermediate	49	2.02	0.88-2.345	0.56
Poor	3	2.33	0.716-2.987	
Mutation				
FLT3+	11	1.355	0.571-3.217	0.491

Multivariate Analysis

Factor	Number	HR	CI	P value
PS				
<2	41			**0.001**
≥2	27	3.327	1.318-8.395	
Post induction remission				
CR	26+20	0.223	0.082-0.47	**0.01**
No CR	22			

(OR= 5.625, 95% CI= 2.106-8.995, p= 0.014) for achievement of remission after induction therapy. On univariate analysis, factors which correlated with OS included PS, post induction remission status and mean inter-cycle delay. Factors significant on univariate analysis were evaluated for multivariate analysis. Post induction remission status (HR=0.223, 95% CI=0.082-0.47, p= 0.01) and PS (HR=3.327, 95% CI=1.318-8.395, p= 0.001) were significant factors on multivariate analysis for OS (Table 5).

Discussion

Our studysuggests that performance status (PS) of the patient at the time of initiation of induction chemotherapy and attainment of complete remission post induction chemotherapy were the only two factors that were significantly associated with improved treatment outcome (better OS). Though we demonstrated statistically significant correlation of FLT3-ITD to poor Event Free survival (EFS) but it did not translate to poor OS due to short follow up of our study.

The prognostic impact of performance status and achievement of complete remission post induction has been highlighted in few studies. [4],[8-10] Bahl et al in their cohort of 480 Indian AML patients found age less than 18 years (HR=0.398, 95% CI= 0.196-0.811, p = 0.008) and PS >2 (HR=1.321, 95% CI= 1.18-1.67, p=0.009) to be significantly associated with OS in multivariate analysis [8]. Chen et al in their cohort of 245 AML patients, reported attainment of CR post induction chemotherapy was significantly associated with better OS (HR=3.72; 95% CI 2.13-6.51, p =<0.001) [4]. The effect of CR on treatment outcome in AML has also been systematically analyzed in 6283 patients by the South West Oncology Group where they concluded that attainment of CR is of unique clinical significance and is significantly (p=0.023) associated with better relapse free survival [9]. In a Danish national acute leukemia registry comprising of 769 AML patients, a statistically significant correlation with OS was demonstrated with attainment of stringent CR (sCR) as compared to non-stringent CR (nCR) [10]. But these researchers did not look for any association of PS at presentation with OS in their analysis.

The prevalence of FLT3-ITD and NPM1 mutations has been reported to be 10.1%-22.6% and 7.5% - 27.5% respectively by various research groups [11-18]. We also found the similar prevalence of these mutations in our cohort of patients (FLT3 - ITD - 16.1%, NPM1-11.7%). The present study demonstrated the prevalence of c- Kit mutation to be 25% (positive in 17 cases) which is higher as compared to that reported by Chinese researchers (4.2%-7.6%) [17-18]. This difference may be explained by the small cohort size and ethnic differences between the two groups. Qin et al. in his cohort of 351 core binding factor acute myeloid leukemia (CBF-AML) reported 36.5% patients positive for c-KIT mutation [19]. Similarly we found 40% patients with CBF-AML to be harboring this mutation. We could not demonstrate any exon 8 mutation in our patient population and all the c-KIT positive patients had exon 17 mutations. Since exon 17 mutations are more frequently associated with t (8,21) while exon 8 with inv 16, the presence of fewer number of inv 16 positive cases (only 3 cases) may have contributed for this observation.None of the 3 patients with inversion 16 showed any c-KIT mutations. The various mutations seen in the exon 17 were K93N, F89L, S92P, A91Qfs, N94S, R137G, D123V, L138P, and P139I. These mutations have not been reported till date in literature.

In our study we noticed statistically significant difference in 2 yr EFS in patients positive for FLT3-ITD mutation (Table 5). However the 2 yr OS did not show significant difference because most of these relapsed patients are presently on 2nd line salvage chemotherapy and awaiting allogenic stem cell transplant. The longer follow up is needed to document significant difference in OS. The poor prognostic value of FLT3-ITD mutation has been reported in several studies [12,15,17,18]. Chen et al in their meta-analysis of the effect of KIT mutations on the complete remission (CR), relapse rates and overall survival (OS) in CBF-AML demonstrated

that there is increased relapse risk (RR [relative risk], 1.43; 95%CI [confidence interval], 1.20-1.70) but no adverse effect on OS (RR, 1.09; 95% CI, 0.97-1.23) and CR rates (OR [odds ratio], 0.95; 95% CI, 0.52-1.74) [20].

Our 2 yr EFS (22.8%) and 2 yr OS (39.6%) is inferior to that reported by other Indian studies [8,15,23,24]. This may be attributed to delay in initiation of induction chemotherapy (median delay 50 days) from the date of diagnosis of the disease due to limited availability of beds for admission (hence long waiting list), delay in arranging finances and donor support for blood transfusions. Thus due to this treatment delay, majority of patients contact some life threatening infection (bacterial/fungal) and complete induction chemotherapy (3+7) could not be administered. Out of the 68 patients who received induction chemotherapy only 48 (70.5%) patients could receive full induction chemotherapy whereas in 20 (29.5%) patients, induction was abbreviated as they developed features of severe sepsis during induction. On the contrary, our induction mortality was very low (4.4%) compared to other centers in the country [8,15,23,24]. This has been possible due to better ICU and nursing care, aggressive management of febrile neutropenia including granulocyte transfusions support.

The main limitation of our study was its small sample size and short follow up due to which our results need to be validated in a larger prospective study.

Conclusion

Performance status at presentation and response to induction chemotherapy are the strongest predictors of survival in the AML patients. Early diagnosis and prompt initiation of therapy is the key to improve outcome in AML patients. The independent prognostic significance of depth of response to induction chemotherapy (CR vsi CRvs IF) strongly supports the use of Minimal Residual Disease (MRD) monitoring in AML treatment algorithms.

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Conflicts of Interest: None.

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