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Original Article

Brain and Acute Leukemia, Cytoplasmic Gene Overexpression as a Prognostic Factor in Egyptian *De novo* Adult Acute Myeloid Leukemia Patients

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Abstract

Background: Brain and acute leukemia, cytoplasmic (BAALC) gene is identified on chromosome 8q22.3 and implicated in normal hematopoiesis. BAALC gene overexpression is associated with poor outcome. **Methods:** We aimed to evaluate BAALC expression in *de novo* Egyptian acute myeloid leukemia (AML) cases and determine its prognostic value. We recruited 70 patients with *de novo* AML diagnosed and treated at clinical pathology and medical oncology departments, fulfilling inclusion criteria in our prospective study and evaluated BAALC expression level. Patients received induction therapy. The Institutional Review Board approved our study. **Results:** The mean age was 39.2 years ± 11.87, (18–60) with a male/female ratio of 3/2. The cutoff value of BAALC as a prognostic factor was 2.11 with sensitivity (86.1%), specificity (80%), positive predictive value (88.6%), and negative predictive value (76.2%.) ($P < 0.001$), 43 (61.4%) patients had high BAALC expression. Seventy-two percent of patients in the low BAALC group achieved complete remission (CR) compared to 42.1% in high BAALC expression group ($P = 0.03$). Patients with low BAALC (123.1 ± 4.9) had longer mean survival time than high BAALC group (45.85 ± 5.1) ($P = 0.000$). **Conclusion:** High-BAALC expression is an adverse prognostic factor, with a higher risk of relapse, lower CR rates, and lower survival in Egyptian *de novo* AML patients.

Keywords: *Acute myeloid leukemia, adult, brain and acute leukemia, cytoplasmic, de novo, prognostic*

Introduction

Acute myeloid leukemia (AML) is a clonal myeloid neoplasm with myelopoiesis maturation arrest that leads to myeloblasts accumulation in the bone marrow (BM) and/or blood. According to the current WHO classification, myeloblasts must comprise at least 20% of nucleated cells in the BM or blood to establish a diagnosis of AML.[1]

Nowadays, therapeutic options for AML that incorporate therapies targeted at specific dysregulated genetic pathways are available. Therefore, 2008 WHO Classification of AML relies mainly on cytogenetic abnormalities and mutations in three oncogenes (NPM1, FLT3, and CEBPA) for genetic sub-classification.[1]

Deregulation expression of genes involved in cell survival, proliferation and differentiation, e.g., (brain and acute leukemia and cytoplasmic [BAALC]),[2,3] ERG, MN1 and WT1, and EVI1 were identified as the prognostic markers.[4]

BAALC gene identified on chromosome 8q22.3 is implicated in normal hematopoiesis. However, BAALC function in the hematopoietic system and its contribution in leukemogenesis are not fully understood. BAALC blocks myeloid differentiation, thus requiring a second mutation to induce leukemogenesis.[5]

BAALC overexpression is an indicator of AML aggressiveness as it is associated with poor clinical outcome.[6] High-BAALC expression is associated with lower CR rates, shorter event free survival, and shorter overall survival.[7]

Methods

Study design

We carried out this prospective cohort study in the Clinical Pathology Department, Scientific and Medical Research Center and Medical Oncology Department, Faculty of Medicine, from January 2015 and February

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2019. The Faculty of Medicine Institutional Review Board and the Ethical Committee approved this study. We evaluated BAALC expression levels in acute myeloid leukemia patients and assessed its prognostic significance. A total of 70 patients were recruited, out of 107 patients in 12 months, informed consent was obtained from all patients. Furthermore, six individuals matched for age and sex were enrolled as internal control, patient's distribution is shown in Figure 1.

Patient selection

We enrolled in the study *de novo* adult AML patients aged >18 years old with normal liver, kidney and cardiac function tests with no concurrent malignancy and PS ≤2. We excluded patients with secondary or relapsed AML or AML (M3).

Methods of brain and acute leukemia and cytoplasmic detection

We withdrew 2 ml of venous blood aseptically from each patient by venipuncture into EDTA vacutainer for ESR. 2 ml of blood was directly used for RNA extraction.

Molecular detection of brain and acute leukemia and cytoplasmic RNA gene expression

RNA extraction from whole blood

We used Pure Link RNA Mini Kit (Life Technologies, USA) to purify RNA from anticoagulated BM sample.

Reverse-transcription polymerase chain reaction of total RNA to cDNA

To synthesize single-stranded cDNA from total RNA, we use the high capacity cDNA reverse transcription kits:

We prepared the 2 × Reverse Transcription Master Mix as per 20 µl reaction.

Real-time reverse transcription polymerase chain reaction

Using Taqman gene expression assay.

Principle

Fluorescent dye intercalates into the amplification product, which enables the rapid analysis of target DNA during the polymerase chain reaction (PCR) process.

The real-time polymerase chain reaction

Using the stratagene m × 3005p quantitative PCR system.

Interpretation of results

We normalized the transcription levels of target genes to those of B-actin (using a reference gene for accounting for the variability of cDNA amount in each sample).

Target genes expressed and presented as fold change of gene expression relative to controls. BAALC expression was positive if their expression level was one log higher than the mean level of expression reported for the control group, so the mean level for control was 1, samples were positive if expression level was more than 2.[8]

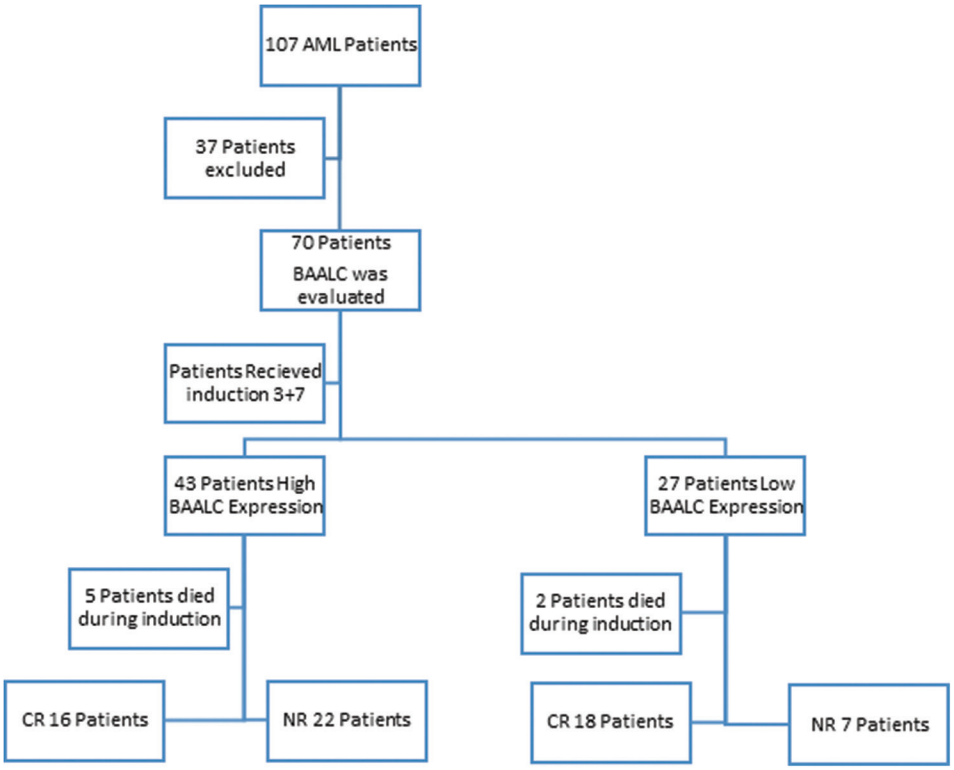

Figure 1: Patients distribution

Assessment

We assessed patients demographics, clinical and laboratory data at the diagnosis (complete blood count [CBC], blood film, kidney function tests, serum uric acid, electrolytes level, liver function tests, coagulation profile, virology (HCV Ab, HBs Ag, HBc Ab, and HIV Ab)), and CSF cytological analysis (if needed). Specific investigations include BMA, immunophenotyping, karyotyping, and reverse transcriptase PCR for BAALC gene expression. We treated the patients with induction regimen (3 + 7 protocol) consisting of cytarabine (100 mg/m^2/24 h) continuous infusion daily for seven consecutive days, combined with doxorubicin (30 mg/m^2/24 h) for 3 days. An induction protocol consisting of (2 + 14 protocol) (cytarabine 10 mg/m^2/12 h) daily for 14 days combined with 2 days of doxorubicin (25 mg/m^2), was offered to patients who are over 60 years or to those who are between 55 and 60 with multiple comorbidities. We evaluated CBC and BM aspirate on day 14, 28 to evaluate the remission state.

The patient achieved CR if BM was normocellular, containing <5% blast cells and peripheral blood (PB) with at least 1 × 109/L neutrophils and ≥100 × 109/L platelets (PLTs). Remission failure included either partial remission (PR: Defined as 5%–15% blast cells), resistant disease (RD: Defined as >15% blasts in BM), or induction death (ID: Defined as related to treatment or hypoplasia). We followed patients for 3 years to evaluate the survival.

Consolidation therapy: 3–4 cycles of high dose Ara-C (1 g/m^2/12 h at days 1, 3, 5) postremission.

Statistical analysis

We used version 23.0. of IBM SPSS statistics (IBM Corp., Armonk, NY, USA); percentage analysis was done for categorical data; mean and standard deviation for continuous variables; survival was estimated using the Kaplan–Meier method. We evaluated the relationship between different prognostic and predictor variables with survival using the log-rank test. Independent prognostic variables affecting survival were evaluated using Cox-regression analysis. Tests were two-sided. $P \leq 0.05$ was considered as statistically significant, $P \leq 0.001$ as considered as highly significant.

Results

The present study included 70 patients. Forty-three patients (61.4%) were males, 27 females, and their ages ranged from 19 to 58 years, with a mean of 39.2 years ± 11.87.

Patients' characteristics are described in Table 1, where 22 patients had cytogenetic abnormalities, 6 patients of M2 show t (8; 21), 7 patients of M4 show inv (16), 3 patients of M1 and 2 patient from M5 show tri (8), and 4 patients of M5 show t (11;12).

Table 1: Clinical and laboratory data of studied acute myeloid leukemia patients

Variable	AML patients (*n*=70), *n* (%)
Bone aches	65 (92.9)
Fatigue	57 (81.4)
Gum hypertrophy	49 (70)
Purpura	51 (72.9)
Bleeding	50 (71.4)
Fever	50 (71.4)
Splenomegaly	11 (15.7)
Hepatomegaly	11 (15.7)
Lymphadenopathy	6 (8.6)
TLC (×10^9 /L), median (range)	48.70 (12- 161)
Hb (g/dl), mean±SD (range)	6.30±1.7 (3.4- 9.5)
PLT (×10^9/L), median (range)	28 (5- 100)
PB blasts (%), mean±SD (range)	58.05±17.05 (29-90)
BM blasts (%), mean±SD (range)	74.23±13.18 (52- 95)
ESR (mm/h), mean±SD (range)	111.1±17.16 (90- 150)
LDH (IU/L), mean±SD (range)	785.5±217.62 (420- 1200)
FAB	
With myeloid differentiation	21 (30)
M1	3 (4.3)
M2	18 (25.7)
With monocytic differentiation	49 (70)
M4	22 (31.4)
M5	27 (38.6)
Cytogenetics	
Normal	48 (68.6)
Abnormal	22 (31.4)
Risk	
Favorable	13 (18.6)
t (8;21)	6 (8.6)
inv (16)	7 (10)
Intermediate	53 (75.7)
Normal	48 (68.6)
Tri 8	5 (7.1)
Adverse	
t (11;12)	4 (5.7)

AML: Acute myeloid leukemia, TLC: Total leukocyte count, HB: Hemoglobin, PB: Peripheral blood, PLT: Platelet, BM: Bone marrow, ESR: Erythrocyte sedimentation rate, LDH: Lactate dehydrogenase, SD: Standard deviation, FAB: The French-American-British classification of AML

Comparison between cytogenetic risk group AML patients as regard laboratory data showed that Hb, BM blasts, lactate dehydrogenase (LDH), total leukocyte count (TLC), PLT and BAALC were the statistical difference between different cytogenetic risk groups, as shown in Table 2.

ROC curve for BAALC as a prognostic factor for survival in AML patients is shown in Figure 2 with sensitivity (86.1%), specificity (80%) with positive predictive value (88.6%) and negative predictive value (76.2%.) with $P = 0.000$ with cutoff value 2.11, where patients were classified into two groups based on BAALC value, also BAALC sensitivity

Table 2: Comparison between cytogenetic risk and laboratory data, brain and acute leukemia, cytoplasmic among acute myeloid leukemia patients

Variable	Normal cytogenetic (*n*=48)	Favorable (*n*=13)	Intermediate and adverse (*n*=9)	*P*
Hb: Mean±SD	5.69±1.21	7.55±1.96	7.00±2.53	0.002*
BM blast: Mean±SD	82.13±9.86	61.91±9.49	64.17±9.66	0.000*
LDH: Mean±SD	873.13±209.38	634.55±115.63	586.33±33	0.000*
ESR: Mean±SD	118.21±18.87	127.55±9.53	127.67±11.94	0.172
TLC: Median (range)	55 (15- 150)	27 (14- 50)	35 (12- 161)	0.001*
PLT: Median (range)	24 (6- 92)	72 (35- 100)	48.50 (5- 88)	0.000*
PB blasts: Median (range)	54 (29- 90)	60 (29- 83)	70 (37- 84)	0.365
BAALC: Median (range)	3.21 (1.05- 13.76)	1.13 (0.80- 10.43)	1.18 (0.86- 3.21)	0.000*

AML: Acute myeloid leukemia, TLC: Total leukocyte count, HB: Hemoglobin, PB: Peripheral blood, PLT: Platelet, BM: Bone marrow, ESR: Erythrocyte sedimentation rate, LDH: Lactate dehydrogenase, SD: Standard deviation, BAALC: Brain and Acute Leukemia, Cytoplasmic. *Statistically significant

Table 3: Sensitivity and specificity of brain and acute leukemia, cytoplasmic as a prognostic factor for survival

Crosstab				
BAALC overexpression	Variables	Survival		Total
		Die	Survive	
BAALC2.11				
>2.11	Count	38	5	43
	Percentage within BAALC2.11	84.4	11.6	100.0
	Percentage within survival	86.1	20.0	62.5
≤2.11	Count	7	20	27
	Percentage within BAALC2.11	25.9	74.1	100.0
	Percentage within survival	15.6	80.0	37.5
Total	Count	45	25	70
	Percentage within BAALC2.11	64.3	35.7	100.0
	Percentage within Survival	100.0	100.0	100.0

BAALC: Brain and acute leukemia, cytoplasmic

AUC				
Test result variable(s): BAALC				
Area	SE	Asymptotic significance	Asymptotic 95% CI	
			Lower bound	Upper bound
0.832	0.060	0.000	0.715	0.949

AUC=0.83. CI=0.71- 0.94. CI: Confidence interval, SE: Standard error, BAALC: Brain And Acute Leukemia, Cytoplasmic, AUC: Area under the curve

and specificity as a prognostic factor for survival is shown in Table 3.

BAALC high and low groups were compared using the Mann–Whitney U test regard age, laboratory and clinical data and response to therapy; our results showed HB, BM blast, LDH, TLC, PLT, gum hypertrophy, bleeding, purpura, cytogenetics, and response to induction therapy differ significantly between BAALC high and low groups, as shown in Table 4.

Treatment

Different responses to induction therapy between both BAALC high or low is shown in Table 4, 66 AML patients received induction chemotherapy "3 + 7" while 4 received 2 + 14 protocol. BMA was used to assess response at day 14, it was done for 65 patients (5 patients had induction death). At D28, the response was assessed using BMA, 63 patients were evaluated, 2 patients lost after D14 evaluation (induction death).

Factors that affected survival significantly on univariate analysis were entered for multivariate analysis in

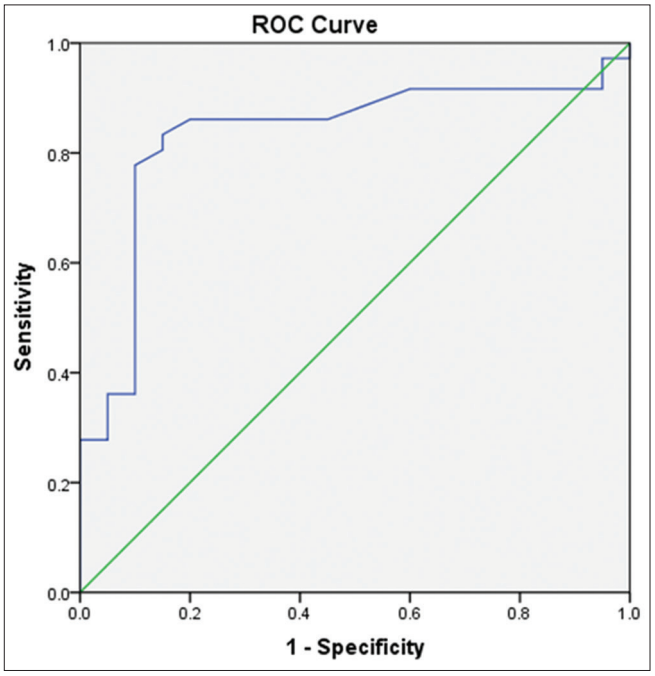

Figure 2: Receptor operating characteristic curve for brain and acute leukemia, cytoplasmic as a prognostic factor for survival in acute myeloid leukemia patients

cox-proportional hazard model. There was a statistically significant association between survival and gum hypertrophy, i.e., patients with gum hypertrophy are at a risk of dying 2.2 more than those with no gum hypertrophy, cytogenetics, i.e., patients with abnormal cytogenetics carry less risk 0.45 to die than those with normal cytogenetics, laboratory data, i.e., patients with low hemoglobin level,

increased BM blasts, increased LDH level, higher TLC, lower PLT count, increased PB blasts, and high BAALC expression are at risk to die [Table 5].

When we evaluated mean overall survival time according to chemotherapy response, cytogenetics and BAALC among studied AML patients by Kaplan–Meier test, we found that mean survival time for patients who achieve complete remission (CR) (121.1 ± 4.9) was statistically significantly longer than those who not achieve CR (34.2 ± 2.8) (log-rank test = 62.62, P = 0.000). Mean survival time for cytogenetically normal AML patients (60.25 ± 7.13) was shorter than favorable group (114.00 ± 8.64) and (patients with abnormal cytogenetics in intermediate and poor-risk groups (107.16 ± 16.71) (log-rank test = 10.83, P = 0.004), also patients with low BAALC (123.1 ± 4.9) had longer mean survival time than patients with high BAALC (45.85 ± 5.1) (log-rank test = 31.20, P = 0.000) as shown in Table 6 and Figure 3.

Forty-five patient died 45/70 (64.3%). 3 (4.3%) patients died initially before starting induction therapy related to disease (early death), 4 (5.7%) patients died throughout induction chemotherapy period (induction death), 7 (10%) died during consolidation due to chemotherapy toxicity, and 29 (41.4%) patients died as a result of salvage chemotherapy toxicity in nonresponding patients, cause of death was mainly toxicity of chemotherapy (septic shock, heart failure, acute respiratory distress syndrome, and cardiogenic shock), in our study causes of early deaths in our study were related to disease progression (i.e., septic shock, DIC, cerebral haemorrhage and multiorgan failure).

Concerning toxicity; nearly all patients developed variable degrees of haematological toxicities, there was no difference regard toxicity pattern between both BAALC high and low group, although sepsis was numerically more common during induction in BAALC high group. Toxicity was listed in Table 7.

Discussion

In this study, we analyzed BAALC gene expression in 58 adult *de novo* AML patients (18–60 years) and evaluated its prognostic significance.

Typically, BAALC mRNA isn't detected in normal individuals; there was a statistically significant difference in expression between patients group and control, similar to what was reported by other studies.[2,9]

We found no correlation between age and BAALC gene expression, that agreed with what reported in other studies by Bienz *et al*.,[10] and Metzeler *et al*.[4] That differs from what was stated by Rashed *et al*.,[11] who detected a significant correlation between high BAALC gene expression and age. Patients older than 45 years had higher High BAALC expression. To confirm such an association, larger sample size may be needed.

BAALC gene expression no significant association different between sex, similar to what was declared in other studies.[7,11,12]

Patients in normal cytogenetic risk group had higher BAALC overexpression than the other two groups; this concurs with Zhou *et al*.[13]

We found that patients with CN-AML had higher (TLC, LDH level and blast cell count) and lower (PLT count and Hb level) that were statistically significant compared to the other groups. In patients with CN-AML median BAALC was 3.21, that was a statistically significant difference than the other two groups. This agreed with Zhou *et al*.,[13] where BAALC median was 3.74.

Our cut off value for BAALC gene expression was > 2.11 with sensitivity 86.1% and specificity 80%, near to what stated by Zhou *et al*., where the cut-off value was > 2.35 with sensitivity 55% and specificity 100.

No significant difference between both BAALC high expressed and low expressed patients regard age distribution, this agrees with Soliman *et al*.,[14] in contrary to Zhou *et al*.,[13] Rashed *et al*.,[11] who recorded that low BAALC expresser patients were significantly younger than high BAALC expresser patients.

Patients with low BAALC expression had significant lower BM blasts than in high BAALC expression group that work in with Qi *et al*.,[15] Zhou *et al*.,[13] Schwind *et al*. did not confirm these findings,[16] and Weber *et al*.,[7] who did not found the difference in BM blasts between low BAALC expressed and high BAALC expressed groups. We could be owed this to the differences in the distribution of AML subtype or ethnicity.

Regard correlation between BAALC expression and response rate was found that patient with low BAALC expression achieved higher CR rate (70%) in comparison to patients with high BAALC (40%), this agrees with El-Sharnouby *et al*.,[17] and Yahya *et al*.,[18] who found that frequency of CR was higher in low BAALC expresser patients than in high expressers 71.4% versus 50% and 73.9% versus 22.7% respectively. Also, patients with high BAALC expression had a significantly worse clinical outcome than low expressers.

Regard survival, we found low BAALC expression patients had significantly longer overall survival than high BAALC expression patients (123 vs. 45 weeks respectively), and this came in concordance with Zhou *et al*.,[13] and Yahya *et al*.,[18] who shows superior overall survival (15.02 vs. 7.02 months) in low BAALC expressers.

In concordance with what stated by Bienz *et al*.,[10] Baldus *et al*.,[2] Langer *et al*.,[3] Langer *et al*., 2009[19];

Table 4: Comparison between age, laboratory and clinical data, response to therapy in relation to brain and acute leukemia and cytoplasmic

Variable	BAALC		Test	*P*
	>2.11 (*n*=43)	≤2.11 (*n*=27)		
Age: Mean±SD	38.03±12.76	42.24±9.96	*t*=1.29	0.202
Hb: Mean±SD	5.51±1.26	7.33±1.77	*t*=4.46	0.000*
BM blasts: Mean±SD	85.20±6.09	61.29±6.27	*t*=14.06	0.000*
LDH: Mean±SD	924.74±164.47	580.19±79.66	*t*=8.96	0.000*
ESR: Mean±SD	121.72±17.26	119.85±35	*t*=0.38	0.699
TLC: Median (range)	60 (33- 161)	29 (12- 52)	MW=4.68	0.000*
Plt: Median (range)	20 (5- 40)	60 (30- 100)	MW=5.90	0.000*
PB blasts: Median (range)	58 (29- 90)	60 (29- 84)	MW=0.24	0.806
Sex, *n* (%)				
Female (27)	17 (63)	10 (37)	χ^2=0.02	0.888
Male (43)	26 (60.5)	17 (39.5)		
Fatigue, *n* (%)				
Yes (57)	35 (61.4)	22 (38.6)	Fisher exact test	1
No (13)	8 (61.5)	5 (38.5)		
Fever, *n* (%)				
Yes (50)	31 (62)	19 (38)	χ^2=0.141	0.708
No (20)	12 (60)	8 (40)		
Bone ache, *n* (%)				
Yes (64)	40 (64.5)	24 (37.5)	χ^2=0.287	0.592
No (6)	3 (50)	3 (50)		
Gum hypertrophy, *n* (%)				
Yes (49)	41 (83.5)	8 (16.5)	χ^2=27.25	0.000*
No (21)	2 (6.7)	19 (93.3)		
Bleeding, *n* (%)				
Yes (50)	36 (72)	14 (28)	χ^2=5.97	0.015*
No (20)	7 (37.5)	13 (62.5)		
Purpura, *n* (%)				
Yes (51)	36 (70.6)	15 (29.4)	χ^2=7.4	0.006*
No (19)	7 (36.8)	12 (63.2)		
Splenomegaly, *n* (%)				
Yes (11)	7 (63.6)	4 (36.4)	χ^2=0.07	0.778
No (59)	36 (61)	23 (39)		
Hepatomegaly, *n* (%)				
Yes (11)	7 (63.6)	4 (36.4)	χ^2=0.07	0.778
No (59)	36 (61)	23 (39)		
LN, *n* (%)				
Yes (6)	4 (66.7)	2 (33.3)	χ^2=0.71	0.397
No (64)	39 (60.9)	25 (39.1)		
Cytogenetics, *n* (%)				
Abnormal (22)	3 (13.6)	19 (86.4)	χ^2=26.80	0.000*
Normal (48)	40 (83.3)	8 (16.7)		
Induction protocol (70), *n* (%)				0.33
3+7 (66 [94.3%])	39 (90.7)	27 (100)		
2+14 (4[5.7%])	4 (9.3)	0 (0)		
Total 70 (100%)	43 (100)	27 (100)		
BM D14				0.22
Evaluated patients (65[92.9%])				
Unevaluated patients (5[7.1%])				
Blasts % (median, range) (0- 40)	1.5 (0- 12)	5 (0- 40)		

Contd...

Table 4: Contd...

Variable	BAALC		Test	*P*
	>2.11 (*n*=43)	≤2.11 (*n*=27)		
BM D28				
Evaluated patients [63 (90%)]				
Unevaluated (7 [10%])				
Cellularity, *n* (%)				0.88
Normocellular (39[62%])	24 (63.1)	15 (60)		
Hypocellular (12 [19%])	7 (18.4)	5 (20)		
Hypercellular (12 [19%])	7 (18.4)	5 (20)		
Total	38 (100)	25 (100)		0.07
Blasts % (median, range) 2 (0- 21)	2 (0-21)	3 (1-20)		
Induction response (*n*=63), *n* (%)				
CR (34[54%])	16 (42.1)	18 (72)		0.03
Not in CR (29 [46%])	22 (57.9)	7 (28)		
Total	38 (100)	25 (100)		

ANOVA, *t*: *T*-test, MW: Mann- Whitney-U test. AML: Acute myeloid leukemia, TLC: Total leukocyte count, HB: Hemoglobin, PB: Peripheral blood, PLT: Platelet, BM: Bone marrow, ESR: Erythrocyte sedimentation rate, LDH: Lactate dehydrogenase, SD: Standard deviation, BAALC: Brain and Acute Leukemia, Cytoplasmic, LN: Lymphadenopathy

Table 5: Association between survival and demographic, clinical and laboratory data among studied acute myeloid leukemia patients

Variable	Survival		*P*±RR (95% CI)
	Die (45)	Survive (25)	
Sex, *n* (%)			
Female (27)	19 (70.4)	8 (29.6)	0.625 RR 1.1 (0.74- 1.62)
Male (43)	26 (60.5)	17 (39.5)	
Fatigue, *n* (%)			
Yes (57)	36 (63.2)	21 (36.8)	0.96 RR 1.0 (0.61- 1.66)
No (13)	9 (69)	4 (31)	
Fever, *n* (%)			
Yes (50)	32 (64)	18 (36)	0.96 RR 0.99 (0.64- 1.51)
No (20)	13(65)	7 (35)	
Bone ache, *n* (%)			
Yes (64)	42 (65.6)	22 (34.4)	0.53 RR 1.3 (0.48- 3.55)
No (6)	3 (50)	3 (50)	
Gum hypertrophy, *n* (%)			
Yes (49)	37 (75.5)	12 (24.5)	0.003* RR 2.2 (1.08- 4.73)
No (21)	8 (38)	13 (62)	
Bleeding, *n* (%)			
Yes (50)	33 (66)	17 (34)	0.86 RR 1.04 (0.66- 1.61)
No (20)	12 (60)	8 (40)	
Purpura, *n* (%)			
Yes (51)	33 (64.8)	18 (35.2)	0.68 RR 1.09 (0.68- 1.75)
No (19)	12 (63.2)	7 (36.8)	
Splenomegaly, *n* (%)			
Yes (11)	7 (63.6)	4 (36.4)	0.87 RR 1.04 (0.62- 1.73)
No (59)	38 (64.4)	21 (35.6)	
Hepatomegaly, *n* (%)			
Yes (11)	7(63.6)	4 (36.4)	0.87 RR 1.04 (0.62- 1.73)
No (59)	38 (64.4)	21 (35.6)	
LN, *n* (%)			
Yes (6)	4 (66.7)	2 (33.3)	0.44 RR 1.27 (0.78- 2.07)
No (64)	41 (64.1)	23 (35.9)	

Contd...

Table 5: Contd...

Variable	Survival		*P*±RR (95% CI)
	Die (45)	Survive (25)	
Cytogenetics, *n* (%)			
Abnormal (22)	8 (36.4)	14 (63.6)	0.000* RR 0.45 (0.23- 0.89)
Normal (48)	37 (77.1)	11(22.9)	
Hb (g/dl): Mean±SD	5.72±1.4	7.05±1.82	0.004*
BM blasts: Mean±SD	81.6±11.01	66.10±10.5	0.000*
ESR: Mean±SD	121.72±17.26	119.85±35	0.699
LDH: Mean±SD	868.75±204.24	663.75±178.35	0.000*
TLC: ($\times 10^9$/L), median (range)	56 (14- 161)	42.50 (12- 136)	0.006*
PLT: ($\times 10^9$/L), median (range)	24 (5- 95)	44 (12- 100)	0.001*
PB blasts: Median (range)	58.50 (29- 90)	59 (29- 84)	0.000*
BAALC: Median (range)	3.32 (0.80- 13.7)	1.21 (0.86- 6.88)	0.000*

t: *T*-test, MW: Mann- Whitney-U test. AML: Acute myeloid leukemia, TLC: Total leukocyte count, HB: Hemoglobin, PB: Peripheral blood, PLT: Platelet, BM: Bone marrow, ESR: Erythrocyte sedimentation rate, LDH: Lactate dehydrogenase, SD: Standard deviation, BAALC: Brain and Acute Leukemia, Cytoplasmic, CI: Confidence interval, RR: Relative risk, LN: Lymphadenopathy. *Statistically significant

Table 6: Mean survival time according to chemotherapy response, cytogenetics and brain and acute leukemia, cytoplasmic among studied acute myeloid leukemia patients by Kaplan- Meier test

	Total (*n*)	Death	Censored (still alive), *n* (%)	Mean survival time (weeks) X±SD	95% CI	Log-rank test	*P*
Chemotherapy response							
No CR	29	29	0 (0.0)	34.2±2.8	28.74- 39.73	62.62	0.000
CR	34	7	27 (79.4)	121.1±4.9	111.48- 130.88		
Overall	63	36	27 (42.9)				
Cytogenetics							
CN-AML	43	30	13 (30.2)	60.25±7.13	46.28- 74.23	10.83	0.004
Favorable	13	2	11 (84.6)	114.00±8.64	97.05- 130.94		
Inter and poor	7	4	3 (42.9)	107.16±16.71	74.40- 139.92		
Overall	63	36	27 (42.9)				
BAALC2.11							
>2.11	39	32	7 (17.9)	45.85±5.1	35.66- 56.04	31.20	0.000*
≤2.11	34	4	20 (83.3)	123.61±4.9	113.93- 133.29		
Overall	63	36	27 (42.9)				

CI: Confidence interval, BAALC: Brain and Acute Leukemia, Cytoplasmic, AML: Acute myeloid leukemia, SD: Standard deviation

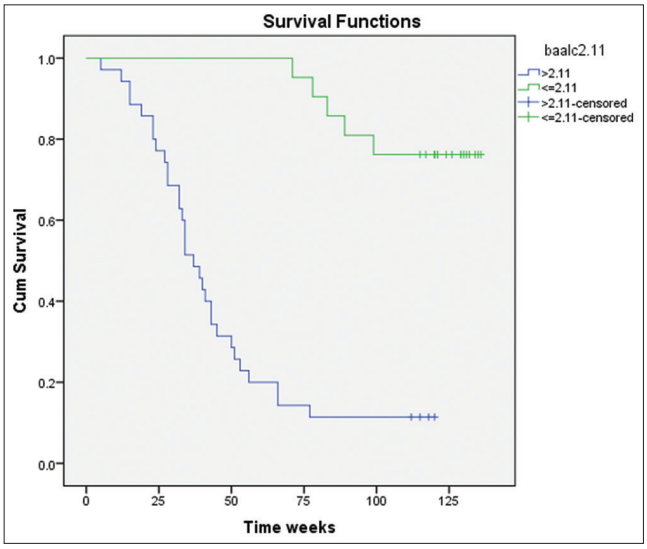

Figure 3: Cumulative survival time according to brain and acute leukemia, cytoplasmic among studied acute myeloid leukemia patients by Kaplan–Meier test

Schwind *et al*.,[16] and Eisfeld *et al*.,[20] we found that The likely hood of death was almost twice in high BAALC expression patients compared to low BAALC expression patients.

Limitation of our study

Risk stratification based on only cytogenetics. Were molecular markers such as FLT3, IDH1, NPM1. We used Doxorubicine as it is the available anthracycline in our institute.

Conclusion

AML patients had increased BAALC gene expression. High BAALC expression is associated with a higher risk of relapse and lower rates of CR. This molecular marker is specific significant associated with response to treatment, disease progression and survival. So its overexpression is a poor prognostic marker, it might be of a potential target for the evolution of new therapies.

Table 7: Toxicities during induction and consolidation therapy

Toxicity type	During induction (*n*=63), *n* (%)	During consolidation (*n*=56), *n* (%)
Hematological toxicity		
Neutropenia		
G3	0 (0)	4 (7)
G4	63 (100)	52 (93)
Anemia		
G3	53 (84.1)	45 (80)
G4	10 (15.9)	11 (20)
Thrombocytopenia		
G3	0 (0)	3 (5.4)
G4	63 (100)	53 (94.6)
Fever and infection		
Neutropenic fever		
G3	55 (87.3)	45 (80)
G4	8 (12.7)	11 (20)
Cannula site infection		
G2	0 (0)	4 (7)
G3	3 (4.8)	3 (5.4)
G4	1 (1.6)	1 (1.8)
Sepsis		
G3	1 (1.6)	4 (7)
G4	7 (11.1)	1 (1.8)
Chest infection		
G3	9 (14.3)	12 (21.4)
G4	3 (4.8)	0 (0)
Soft-tissue infection		
G3	1 (1.6)	2 (3.6)
G4	2 (3.2)	1 (1.8)
Typhlitis		
G3	4 (6.3)	2 (3.6)
G4	2 (3.2)	1 (1.8)
Fungal infection		
G3	2 (3.2)	7 (12.5)
G4	6 (9.5)	4 (7)
Other toxicities		
Gastritis		
G2	15 (23.8)	8 (14.3)
G3	12 (19)	12 (21.4)
Vomiting		
G2	4 (6.3)	4 (7)
G3	2 (3.2)	2 (3.6)
Diarrhea		
G2	3 (4.8)	4 (7)
G3	2 (3.2)	0 (0)
Liver enzymes increased		
G2	2 (3.2)	5 (8.9)
G3	2 (3.2)	1 (1.8)
Blood bilirubin increased		
G2	2 (3.2)	2 (3.6)
G3	3 (4.8)	0 (0)

According to CTCAE Version 5.0. CTCAE: Common Terminology Criteria for Adverse Events

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Conflicts of interest

There are no conflicts of interest.

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