Original Article

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Website: www.ijhonline.org

DOI: 10.4103/ijh.ijh_17_21

Impact of aberrant antigens expression on remission rate after first induction course of chemotherapy in *de novo* adult acute myeloid leukemia

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Abstract:

BACKGROUND: Aberrant antigen expression is an unexpected antigen that is detected on lineage in question without alteration of lineage definition. Immunophenotypic aberrancies are thought to predict treatment outcome in acute myeloid leukemia (AML). Some studies reported an adverse prognostic association, while others failed to show any association.

AIM: To determine percentage of lymphoid antigens expression in adult AML patients and correlate them with hematological parameters and response to induction chemotherapy protocol.

SUBJECTS AND METHODS: Peripheral blood and bone marrow fresh samples from 81 cases of *de novo* AML were included in this study from November 2018 to October 2019. Hematological parameters were obtained from patients' medical records. Aberrant antigens expression was detected using flow cytometry at the diagnosis. Patients were evaluated after one cycle of chemotherapy regarding remission status.

RESULTS: Out of 81 patients, 60 patients had completed data for evaluation. CD7, CD19 expression, and co-expression of CD7 and CD2 were found in 60%, 10.7%, and 10.7% of patients, respectively. Statistically significant associations were found between initial hemoglobin level and aberrant expression as patients with aberrant expression have higher hemoglobin level than patients without aberrant expression. Complete remission was achieved in 29 out of 60 patients (48.3%) with standard 3 and 7 protocol, whereas 31 patients did not achieve complete remission. There is no statistically significant association between aberrant expression and treatment response to the first cycle of chemotherapy protocol ($P > 0.05$).

CONCLUSIONS: CD7 is the most frequent aberrant antigen expressed in this Iraqi AML patient group. Hemoglobin level was higher in patients with aberrant expression. No significant association between aberrant expression and response to the first cycle of induction.

Keywords:

Aberrant, acute myeloid leukemia, flow cytometry, immunophenotype

Introduction

Aberrant antigen expression is defined as expressing an antigen that is unexpected to be detected in a certain lineage, it should not affect lineage definition.[1]

Immunophenotypic aberrancies were thought to be predictable of treatment outcome in acute myeloid leukemia (AML). Some studies reported an adverse prognostic impact, while others failed to show any association, yet some antigens may deserve further attention because their expression may be related to survival.[2]

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Submission: 26-05-2021
Revised: 29-05-2021
Accepted: 22-09-2021
Published: 01-12-2021

How to cite this article: Hussein GA, Jawad AM. Impact of aberrant antigens expression on remission rate after first induction course of chemotherapy in *de novo* adult acute myeloid leukemia. Iraqi J Hematol 2021;10:118-22.

The study aimed to explore the frequency of lymphoid aberrant antigen expression in a sample of novo Iraqi adult AML patients and to define any association between aberrant expression and laboratory parameters at presentation and to assess any association of aberrant expression with remission rate after first cycle of classical 3 + 7 induction chemotherapy.

Subjects and Methods

Study design

This is a cohort study with data obtained from January 2018 to October 2019. It is carried out in Hematology Center/Medical City Campus/Baghdad-Iraq. The study was approved by the Scientific Council of Internal Medicine/Iraqi Council for Medical specialization. Verbal consent was taken from the patients to collect their data.

Patients

A total of 81 patients who were diagnosed with *de novo* AML (41 male patients and 40 female patients) were enrolled in this study. Seventeen patients died after finishing induction chemotherapy and before bone marrow assessment for induction remission. They were excluded from the evaluation. Four patients lost follow-up and were excluded from the study.

Exclusion criteria

- Age <15 years old
- Acute promyelocytic leukemia
- Secondary AML
- Patients who received protocol other than 3 + 7 induction chemotherapy
- Patients who died after induction chemotherapy and before bone marrow assessment for induction remission
- Patients who lost follow-up after diagnosis and treatment.

Diagnosis and definitions

The diagnosis of AML was based on bone marrow and peripheral blood morphology with blast percentage more than 20% and flow cytometry on bone marrow or peripheral blood sample by hematopathologist where the leukemic blast cells were positive for markers specific for myeloid lineage (MPO, CD13, CD33, CD117, CD11c, CD14, and CD64). Aberrant antigens expression were detected by multi-parameter flow cytometric analysis using flow cytometer (BD FACSCanto II) of bone marrow aspirates or peripheral blood samples collected in Ethylenediaminetetraacetic acid (EDTA) tubes. Aberrant antigen expression was defined as expression of an unexpected antigen on the lineage in question, without altering the lineage definition.

Data collection

Hematological parameters including hemoglobin, white blood cell (WBC), platelets count using automated device, bone marrow blast cell percentage and immunophenotypic features of bone marrow or peripheral blood samples were obtained from the patients' medical records. The patients were evaluated by bone marrow and peripheral blood examination for complete remission after induction chemotherapy with classical 3 and 7 protocol.

Treatment and follow-up

Patient received classical 3 + 7 chemotherapy protocol (cytarabine 100 mg/m^2 continuous infusion for 7 days with daunorubicin 60 mg/m^2 or doxorubicin 30 mg/m^2 or idarubicin 12 mg/m^2 for 3 days). Complete remission was defined as the presence of <5% of blasts in the bone marrow aspirate 3–4 weeks after the induction therapy was initiated, along with the absence of blasts in peripheral blood, no extramedullary leukemia infiltrations, an absolute neutrophil count $\geq 1.5 \times 10^9$/L, and platelet counts $\geq 100 \times 10^9$/L. Patients who meet the marrow criteria, but do not achieve full peripheral count regeneration, are considered to have complete remission with incomplete count recovery (CR), i.e., either the neutrophil or platelet count has failed to reach the level required for the definition of count recovery CR.[3] The patients were stratified into two groups: Patients without aberrant markers and patients with aberrant markers. The study is designed to look for differences in the initial hematological parameters and complete remission achievement between these two groups.

Statistical analysis

Statistical analysis was carried out using the SPSS software version 25 (International Business Machines Corporation (IBM), an American multinational technology corporation headquartered in New York). The categorical variables were presented as frequencies and percentages. The continuous variables were presented as means ± standard deviation (SD) *t*-test was used to find mean differences between two variables. Mann-Whitney test was used instead of *t*-test for variables not normally distributed. One-way analysis of variance was used to find the mean differences among more than two variables. Pearson's Chi-square test was used to find the association between the dependent and independent variables. $P < 0.05$ was considered statistically significant.

Results

This study included 60 Iraqi adult patients with *de novo* AML who finished first induction chemotherapy with 3 and 7 protocols and evaluated for remission status.

The mean age of all patients included in this study was 33.78 ± 13.43 years, with a median of 33.5 years, and a range of 15–65 years old [Table 1]. Gender distribution revealed 33 males and 27 females with a male: female ratio of 1.2:1 [Figure 1].

The mean initial WBC count of all patients included in this study was 48.237 ± 62.8543 SD, with a median of 24 × 10^9/L and a range of 1.1–298 × 10^9/L. The mean initial hemoglobin level of all patients included in this study was 8.498 ± 2.3963 SD, with a median of 8.5 g/dL and a range of 4.2–15 g/dL. The mean initial platelet count of all patients included in this study was 79.77 ± 95.637 SD, with a median of 55.5 × 10^9/L and a range of 9–653 × 10^9/L [Table 2].

The results of immunophenotyping revealed that 28 patients had aberrant gene expression while 32 patients had no aberrant expression. CD7 was the most predominant aberrant marker, 17 out of 28 patients (60.7%) had only CD7 marker, 3 out of 28 patients (10.7%) had CD7 with CD2, 1 out of 28 (3.5%) had CD7 with CD19, 1 out of 28 (3.5%) had CD7 with CD79a. Thus, 22 out of 28 patients (78.5%) expressed CD7. CD19 was expressed as a sole marker in 3 out of 28 patients (10.7%) and one patient had CD19 with CD7. Thus, the total expression of CD19 was in four cases. CD2 was expressed as a sole marker in 1 out of 28 patients (3.5%) and three patients having CD2 with CD7. Thus, the total expression of CD2 was in four cases. Two out of 28 patients (7.1%) had CD56 expression [Figure 2].

The AML patients in this study were divided into two groups according to the presence or absence of aberrant expression by flow cytometry. The first group composed of 28 patients who present with aberrant expression. The second group composed of 32 patients with no aberrant expression [Table 3].

The mean hemoglobin level of patients with aberrant expression was significantly higher than those of patients without aberrant expression [$P < 0.05$; Table 4].

Complete remission after medical therapy was achieved in 29 patients (48%) out of 60 patients with first course of standard 3 and 7 induction chemotherapy. Thirty-one patients (52%) had no response to standard therapeutic regimen. 16 out of 28 patients with the aberrant expression did not respond to treatment and 15 out of 32 patients with no aberrant expression have no response [Table 5]. There was no statistically significant association between aberrant antigen expression and treatment response to the first cycle of chemotherapy ($P = 0.297$). Figure 3 shows the distribution of aberrant antigens expression according to the response to treatment after 3 weeks at the end of induction chemotherapy. 12 out of 28 patients with aberrant antigen had responded to treatment induction therapy. Eight of them had CD7, two patients had CD19 and two patients had both CD7 and CD2. Sixteen patients who had aberrant expression had fail to respond to induction therapy; of them 9 patients had CD7, two patients had CD56, one patient had CD2, one

Table 1: Ages of the patients in the study

	n	Minimum	Maximum	Median	Mean±SD
Age	60	15	65	33.5	33.78±13.430

SD=Standard deviation

Table 2: Initial hematological parameters at diagnosis (total number: 60)

	Minimum	Maximum	Median	Mean±SD
WBC count	1.1	298.0	24	48.237±62.8543
Hemoglobin level	4.2	15.0	8.5	8.498±2.3963
Platelet count	9	653	55.5	79.77±95.637

WBC=White blood cells, SD=Standard deviation

Table 3: Frequencies of aberrant antigens expression in the study

	Frequency (%)
No aberrant expression	32 (53.3)
Aberrant expression	28 (46.7)
Total	60 (100.0)

Table 4: The relation of initial hematological parameters to the aberrant expression

	Aberrancy	*n*	Median	Mean±SD	*P*
WBC count	No	32	25.25	44.538±51.5230	0.894
	Yes	28	19.2	52.464±74.5002	
Hemoglobin level	No	32	7.5	7.731±1.9052	0.011
	Yes	28	9	9.375±2.6241	
Platelet count	No	32	47	63.03±51.738	0.407
	Yes	28	66.5	98.89±127.288	

Mann-Whitney test. WBC=White blood cells, SD=Standard deviation

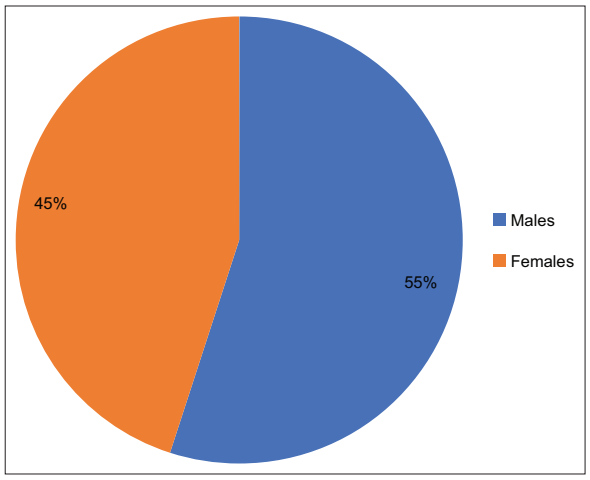

Figure 1: Gender distribution of the patients in the study

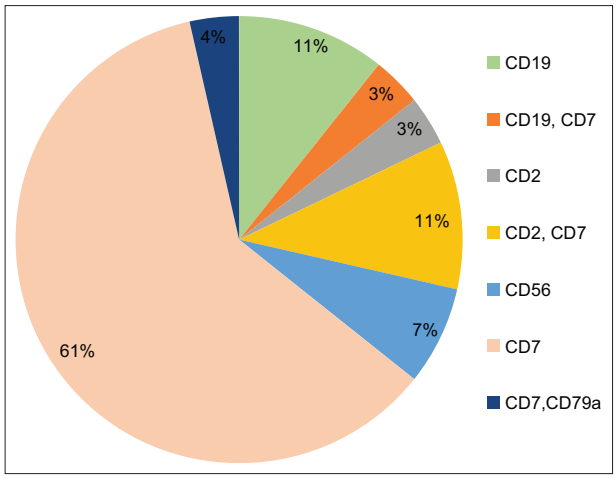

Figure 2: The percentage of each group of aberrancies from 28 AML patients having aberrant antigen expression

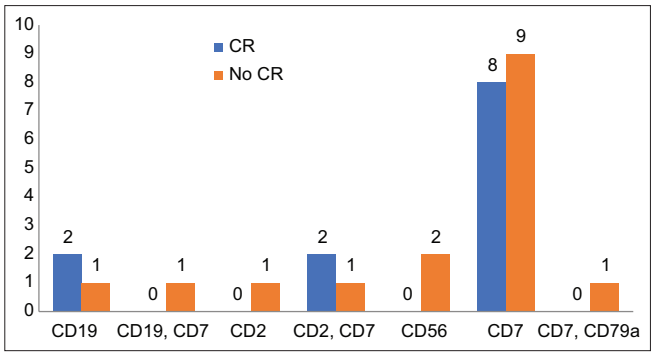

Figure 3: Distribution of each aberrant antigen group in relation to response to induction chemotherapy

Table 5: Relation of aberrant antigen expression to response to induction chemotherapy

	Aberrancy		*P*
	Yes (*n*=28)	No (*n*=32)	
CR (*n*=29)	12	17	0.297
No CR (*n*=31)	16	15	

CR=Complete remission

Table 6: Relation of CD7 expression to response to induction chemotherapy

	CD7 expression		*P*
	Yes (*n*=22)	No (*n*=32)	
Remission status			
CR (*n*=27)	10	17	0.391
No CR (*n*=17)	12	15	

CR=Complete remission

patient had CD19, one patient had both CD2 and CD7, one patient had both CD19 and CD7 and one patient had both CD7 and CD79a.

CD7 was expressed in 22 patients either alone or with other aberrant antigens (the most common expressed aberrant antigen). Twelve patients had no response to induction chemotherapy and 10 patients had CR after the first cycle of induction chemotherapy [Table 6]. There was no statistically significant association between CD7 aberrant antigen expression and treatment response ($P = 0.391$)

Discussion

In this study, the mean age of the patients included was 33.78 ± 13.43 years, with a median of 33.5 years and a range of 15–65 years, which was incomparable with Tawfiq *et al*. 2019,[4] Abdulateef *et al*. 2017,[5] Zaker *et al*. 2010[6] and Gari *et al*. 2008[7] in which the mean age of patients was higher than 40 years. The explanation of this difference in median age is that old age patients who are unfit for classical induction chemotherapy were excluded from this study.

Males made 55% of the AML patients in this study with a male: female ratio 1.2:1 which was in accordance with that reported in Dhahi *et al*. 2012[8] as well as Zaker *et al*. 2010[6] and Kamal *et al*. 2016.[9]

Regarding the frequency of aberrant antigens expression in this study, CD7 was the most predominant aberrant marker (61%) followed by CD19 expression (11%) which was in agreement with Al-Anizi and Al-Mashta 2017,[10] Cruse *et al*. 2005[11] and Rodríguez-Rodríguez *et al*. 2017.[12]

The mean hemoglobin level of patients with aberrant expression was significantly higher than those of patients without aberrant expression while no significant association between aberrant expression and initial WBC count and platelet count. No clear explanation is found in the literature, but it seems that aberrant antigen expression in AML has no clear effect on the proliferative index of blast cells.

CD7 was the most predominant aberrant marker. There was no statistically significant association between CD7 aberrant antigen expression and treatment response to the first course of 3 and 7 protocol. According to Chang *et al*. (Canadian study) in 379 patients, CD7 was the most common aberrant marker (32.2%) and there was no significant association with treatment response.[13] Schwarzinger *et al*. (Austrian study) explored the prognostic significance of surface marker expression on blasts of *de novo* AML patients and there was no effect of CD7 expression on CR rate.[14] de Nully Brown *et al*. (Danish study) examined the prognostic significance of aberrant markers in 117 adult patients with *de novo* AML and the results showed that CD7 expression had no impact on complete remission rate.[15]

There was also no statistically significant association between other aberrant antigen expression and treatment

response in this study. According to Bahia *et al*. (Brazilian study), 35 patients were enrolled for clinical significance of aberrant antigen expression. The result showed that there is no correlation between aberrant expression of CD2, CD7, CD19, and CD56 and complete remission achievement.[16] Shahni *et al*. (Pakistani study) revealed that there is no association between the response to treatment and the expression of aberrant phenotype in 26 AML patients.[17]

Conclusions

CD7 is the most frequent aberrant antigen expressed in this group of Iraqi AML patients. Hemoglobin level was higher in patients with aberrant expression. No significant association between aberrant expression and response to the first cycle of induction.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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