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Role of Dexamethasone in Acute Myeloid Leukemia with High Leucocyte Burden

Haitham ELSheikh, Ayman Fathy, Abdallah Mostafa Mohammed*, Ahmed Embaby
Clinical Hematology Unit, Internal Medicine Department, Faculty of Medicine, Zagazig University, Egypt
***Corresponding author:** Abdallah Mostafa Mohammed, **Mobile:** (+20) 0120876342, **E-Mail:** abdallahmoatafa88@gmail.com

ABSTRACT

Background: Patients with acute myeloid leukemia (AML) with a high white blood cell count are at a significant risk for developing serious complications and passing away before their time. Dexamethasone has been recommended for usage in AML patients because it has a strong inhibitory impact on cytokine production and modulates the inflammatory response.

Objective: To evaluating the effect of adding dexamethasone to induction chemotherapy on the clinical outcome for the first time in Egyptian AML patients with high leucocyte burden.

Patients and methods: This randomized clinical trial included 82 adult patients with AML with high leucocytic count, conducted in Clinical Hematology Unit, Internal Medicine Department, at Zagazig University Hospitals. Patients were divided into two groups; a control group received an induction 3+7 chemotherapy regimen; and a DEXA group received dexamethasone in addition to induction chemotherapy. Patients were followed up after receiving their treatment for a total period of 12 months to estimate survival.

Results: High leucocytic count was positively correlated with peripheral blood blast, AST, creatinine and LDH and negatively correlated with both serum albumin and potassium. Early death was significantly higher in the DEXA group (56.1% vs 24.4% in control group, P= 0.003). Moreover, there was higher death, primary induction failure rates in the DEXA group (P= 0.031 and 0.007 respectively) and lower relapse rates (20% vs 53.3% in control group, P= 0.043). There was statistically significant lower 1-year overall survival in the DEXA group (overall-survival rate 10% vs 21% in the control group, P= 0.003).

Conclusion: Although the use of dexamethasone in AML patients with hyperleukocytosis lowered the relapse rates, it was associated with higher treatment-related mortality and inferior overall survival with no effect on relapse-free survival.

Keywords: Dexamethasone; Acute Myeloid Leukemia; Survival; Leucocyte Burden.

INTRODUCTION

Hematological malignancy known as acute myeloid leukemia (AML) is characterised by the abnormal differentiation and expansion of myeloid lineage cells. Despite contemporary treatment approaches that include intensive chemotherapy and bone marrow transplant, AML still has a 5-year survival rate of less than 30% [(1)].

20% of patients had white blood cell (WBC) counts exceeding 50x109/L at the time of diagnosis. Tumour lysis syndrome (TLS), severe hemorrhage, or metabolic diseases like acute kidney injury (AKI) and disseminated intravascular coagulopathy (DIC), which are further exacerbated by the start of anti-leukemic treatment, increase the likelihood of severe complications in this high-risk situation [(2)]. Additionally, it was shown that the various leucocyte populations and their ratios at the time of diagnosis had a predictive role in AML patients [(3-5)].

Due to early death rates as high as 50% during induction therapy or 30 days after presentation, hyperleukocytosis, particularly if it is accompanied by leucostasis, is a hematologic emergency that requires prompt treatment with cytoreductive drugs. In order to achieve cytoreduction, leukapheresis, hydroxyurea, and harsh chemotherapy can all be employed; nevertheless, the ideal course of treatment is unknown, and innovative treatments are required [(6)].

Glucocorticoids, such as the synthetic steroid dexamethasone (DEXA), can stop the spread of a number of lymphoid cancer types. Despite being acknowledged, the molecular processes by which corticosteroids influence gene expression and protein synthesis are still not entirely understood [(7)].

Dexamethasone may change the early inflammatory response, which is connected to chemo-resistance, and/or improve the sensitivity of AML cells to chemotherapy-induced cell death, which would reduce the chance of leukemic regrowth and recurrence [(2)].

Therefore, this study aimed to detect the effect of adding dexamethasone to induction chemotherapy on the outcome and survival of patients of AML with high leucocyte burden.

PATIENTS AND METHODS

The study was carried out as a randomized clinical trial, single-blind study in Clinical Hematology Unit, Internal Medicine Department, at Zagazig University Hospitals, Egypt. Data were collected from January 2022 to January 2023.

Selection criteria

A total of 82 adult (≥18 years old), newly diagnosed, chemotherapy naïve, non-promyelocytic AML patients with high leucocytic count and good PS (0-2) according to ECOG criteria [(8)], were included in the study.

However, we excluded patients with acute infection, chronic liver disease, collagen vascular

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disease, previous or concomitant other malignancies, HIV infection, and pregnant females.

Steps of performance and techniques

All patients were subjected to proper history taking, and thorough physical examination focusing on the signs and complications of hyperleukocytosis as neurological, retinal, or respiratory affection.

In addition, we performed laboratory investigations as, complete blood count (CBC): The values for TLC count were determined by an automated cell counter together with examination of Leishman-stained peripheral blood smears for differential leucocytic count, along with TLS-screening: calcium, phosphorus and potassium, uric acid, lactate dehydrogenase (LDH), inflammatory markers: ESR and CRP and virology status including: HCV antibody, HBsAg and HIV antibodies. The diagnosis of AML depends on bone marrow aspiration/biopsy and immunostaining with determination of FAB classification and conventional cytogenetics.

Regarding treatment: we divided patients into 2 groups: **The 1st group**: received an induction 3+7 chemotherapy regimen that included doxorubicin at a dose of 30 mg/m^2 of body surface area daily for 3 days, together with a continuous intravenous infusion of cytarabine at a daily dose of 100 mg/m^2 daily for 7 days. **The 2nd group**: received dexamethasone (10 mg twice per day for 3 days) in addition to induction chemotherapy [(2)]**.**

Some patients received additional cytoreductive treatment in the form of hydroxyurea (15-35 mg/m^2/day) according to their WBCS and clinical states and all of them received prophylaxis for tumor lysis syndrome as good hydration and allopurinol, with proper detection and management of chemotherapy and dexamethasone adverse effects as neutropenic fever, infection, need for ICU admission, secondary HTN or DM.

Response to induction therapy was assessed after one or two courses of chemotherapy according to the 2017 ELN recommendations [(9)]**,** and patients who achieved complete remission proceeded to subsequent treatment steps, based on relapse risk and whether an HLA identical donor had been identified or not.

All the patients were followed after receiving their consolidation treatment for a total of 12 months to estimate survival, including the relapse-free survival (RFS) as measured from the time of complete remission evaluation to the date of relapse or death, and the overall survival (OS) as the time interval from diagnosis until death, whatever the cause.

Ethical Consideration:

The academic and Ethical Committee of Zagazig University approved the project (IRB#: 9213-12-1-2022). All of the subjects' written informed permission was acquired. The Declaration of Helsinki, the World Medical Association's code of ethics for studies involving humans, guided the conduct of this work.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS version 22) was used for data entry and analysis using proper statistical testing as indicated after examining the data distribution for normality using Kolmogorov-Smirnov test. Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test ($\chi 2$) to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). All tests had a two-sided design, and a p-value of 0.05 or less was regarded as statistically significant.

RESULTS

Baseline clinical characteristics:

The present study showed no significant difference between the studied groups regarding age, smoking or gender, performance status scale, anemia, bleeding, gum swelling, body pain and leucostasis. While there was a statistically significant difference regarding presence of LN swelling, fever and sepsis **(Table 1).**

Table (1): Comparison between the studied groups regarding baseline clinicodemographic data

Parameters	Dexamethasone group N=41	Control group N=41	P-Value
	N (%)	N (%)	
Gender:			
Female	**18 (43.9%)**	**16 (39%)**	**0.654**
Male	**23 (56.1%)**	**25 (61%)**	
Smoking	**4 (9.8%)**	**7 (17.1%)**	**0.331**
PS			
0	**29 (70.7%)**	**25 (61%)**	
1	**12 (29.3%)**	**11 (26.8%)**	**0.101**
2	**0 (0%)**	**5 (12.2%)**	
Anemia	**41 (100%)**	**36 (87.8%)**	**0.055**
Bleeding	**10 (24.4%)**	**10 (24.4%)**	**1**
Gum swelling	**1 (2.4%)**	**4 (9.8%)**	**0.359**
LN swelling	**4 (9.8%)**	**14 (34.1%)**	**0.008**
Fever, sepsis	**4 (9.8%)**	**11 (26.8%)**	**0.046**
Body pain	**2 (4.9%)**	**2 (4.9%)**	**1**
Extramedullary	**21(51.0%)**	**19 (46.3%)**	**0.143**
Leucostasis	**21 (51.2%)**	**19 (46.3%)**	**0.143**
	Mean ± SD	**Mean ± SD**	**P**
Age (year)	**47.15 ± 13.02**	**44.41 ± 13.8**	**0.359**
FAB/IPT			
M1	**5 (12.2%)**	**3 (7.3%)**	
M2	**16 (39%)**	**8 (19.5%)**	
M4	**2 (4.9%)**	**12 (29.3%)**	**0.213**
M5	**18 (43.9%)**	**18 (43.9%)**	
Cytogenic risk			
Failure	**13 (31.7%)**	**9 (22%)**	
Favorable	**2 (4.9%)**	**0 (0.0%)**	**0.111**
Intermediate	**26 (63.4%)**	**29 (70.7%)**	
Unfavorable	**0 (0.0%)**	**3 (7.3%)**	

- χ^2chi square, and independent sample t tests were used as indicated.

Regarding initial laboratory data, we found a statistically significant difference between the studied groups regarding calcium and uric acid (significantly higher in the control group), but not for the other laboratory parameters, including FAB/IPT or cytogenetic risk **(Table 2)**.

Table (2): Comparison between the studied groups regarding laboratory data

Parameters	Dexamethasone group (N=41)	Control group (N=41)	p
	Mean ± SD	Mean ± SD	
Hemoglobin (g/dL)	8.08 ± 1.14	8.06 ± 1.65	0.932
Total protein (g/dl)	6.75 ± 0.9	7.01 ± 0.55	0.113
Albumin (g/dl)	3.41 ± 0.59	3.6 ± 0.43	0.1
Sodium (mEq/L)	137.49 ± 2.37	137.66 ± 4.99	0.844
Potassium (mEq/L)	3.73 ± 0.47	3.84 ± 0.51	0.309
Calcium (mg/dL)	8.31 ± 0.84	8.7 ± 0.45	**0.012***
Phosphate (mg/dL)	3.17 ± 1.05	3.01 ± 0.46	0.397
	Median (Range)	Median (Range)	P
Peripheral blasts	60 (45 – 88)	60(35 – 75)	0.271
BM blasts%			
At baseline	70 (42.5 – 77.5)	64 (35 – 81.5)	0.897
After induction	35 (2.5 – 50)	8 (3 – 27.5)	0.306
ALT (U/l)	16(12 – 26)	20(13 – 32)	-0.314
AST (U/L)	23(14 – 25)	23(16 – 27)	0.795
WBCs (mcL)	67(22.6 – 125)	55(29.3 – 72)	0.219
Platelet count (mcL)	30(21 – 71)	35(19 – 53)	0.412
Uric acid (mg/dl)	2.9(2.5 – 3.5)	5 (2.65 – 6.8)	**0.002***
BUN (mg/dL)	12.2(10.4 – 25.5)	13.5(9.75 – 21.5)	0.537
Total bilirubin (µmol/L)	0.5 (0.37 – 0.8)	0.5(0.5 – 0.6)	0.489
Creatinine (mg)	0.7(0.7 – 1.15)	0.7 (0.7 – 0.9)	0.078
CRP (mg/L)	34(15 – 80)	30(18.65 – 96)	0.735
ESR (mm/hr)	78(66 – 86)	85(70 – 96)	0.104
LDH (U/L)	928 (499 – 1008)	696(434 – 1028)	0.233
	N (%)	N (%)	p
HCV	4 (9.8%)	4 (9.8%)	1
HBV	1 (2.4%)	1 (2.4%)	1

Median and (Range): used for non-parametric data. χ^2chi square, Mann Whitney U and independent sample t tests were used as indicated.

Clinical outcome:

Early death and death were statistically significantly more in the dexamethasone group compared to the control group. Shock was the main cause of death in both groups with significantly higher frequency within the dexamethasone group. Relapse rate was significantly lower in the dexamethasone group with higher primary induction failure (PIF) rate. However, there was a statistically non-significant difference between the studied groups regarding complete response, BMT or drugs related adverse effects**,** as demonstrated in **Table 3**.

Table (3): Comparison between the studied groups regarding the clinical outcome

		Dexamethasone group (N=41)	Control Group (N=41)	P-value
		N (%)	N (%)	
Early death	Absent	18 (43.9%)	31 (75.6%)	
	Present	23 (56.1%)	10 (24.4%)	0.003
Death	Absent	8 (19.5%)	17 (41.5%)	
	Present	33 (80.5%)	24 (58.5%)	0.031
Cause of death	ARDS	1(3%)	4 (16.7%)	
	Covid-19	7(21.4%)	1 (4.2%)	
	Sepsis	0 (0%)	7 (29.2%)	<0.001
	Shock	25 (75.8%)	12 (50%)	
Relapse	Absent	8 (80%)	7 (46.7%)	
	Present	2 (20%)	8 (53.3%)	0.043
CR	Absent	31 (75.6%)	26 (63.4%)	
	Present	10 (24.4%)	15 (36.6%)	0.23
PIF	Absent	6 (14.6%)	17 (41.5%)	
	Present	35 (85.4%)	24 (58.5%)	0.007
	Underwent BMT	2 (4.9%)	6 (14.6%)	0.264
	ICU admission	36 (87.8%)	32 (78%)	0.137
Documented microbial infection		30 (75%)	28 (68.2%)	0.616

- χ^2chi square test CR: complete remission, PIF: primary induction failure, ICU: intensive-care unit

High leucocyte burden Clinic-laboratory correlations:

The total leucocytic count had a statistically significant positive linear correlation with peripheral blood blast, AST, blood urea nitrogen and LDH, as well as statistically significant negative correlation with both serum albumin, and potassium **(Table 4, Figure 1)**.

Table (4): Linear correlation between TLC and other studied parameters

Parameter	r	P-value
Age (years)	-0.101	0.365
Performance scale	0.031	0.786
Hemoglobin (g/dl)	0.001	0.996
Platelet count (mcL)	-0.076	0.495
Peripheral blast (%)	**0.335**	**0.002**
Total bilirubin (µmol/L)	-0.112	0.316
Total protein (g/dL)	-0.175	0.116
Serum albumin (g/dL)	**-0.324**	**0.003**
ALT (U/l)	0.001	0.996
AST (U/l)	**0.427**	**<0.001**
BUN (mg/dL)	**0.247**	**0.025**
Creatinine (mg)	**0.44**	**<0.001**
Sodium (mEq/L)	-0.115	0.302
Potassium (mEq/L)	**-0.26**	**0.018**
Calcium (mg/dL)	0.031	0.78
Phosphate (mg/dL)	-0.016	0.884
Uric acid (mg/dL)	0.158	0.157
LDH (U/L)	**0.558**	**<0.001**
CRP (mg/L)	-0.012	0.916
ESR (mm/hr)	0.213	0.054

r Spearman rank correlation coefficient

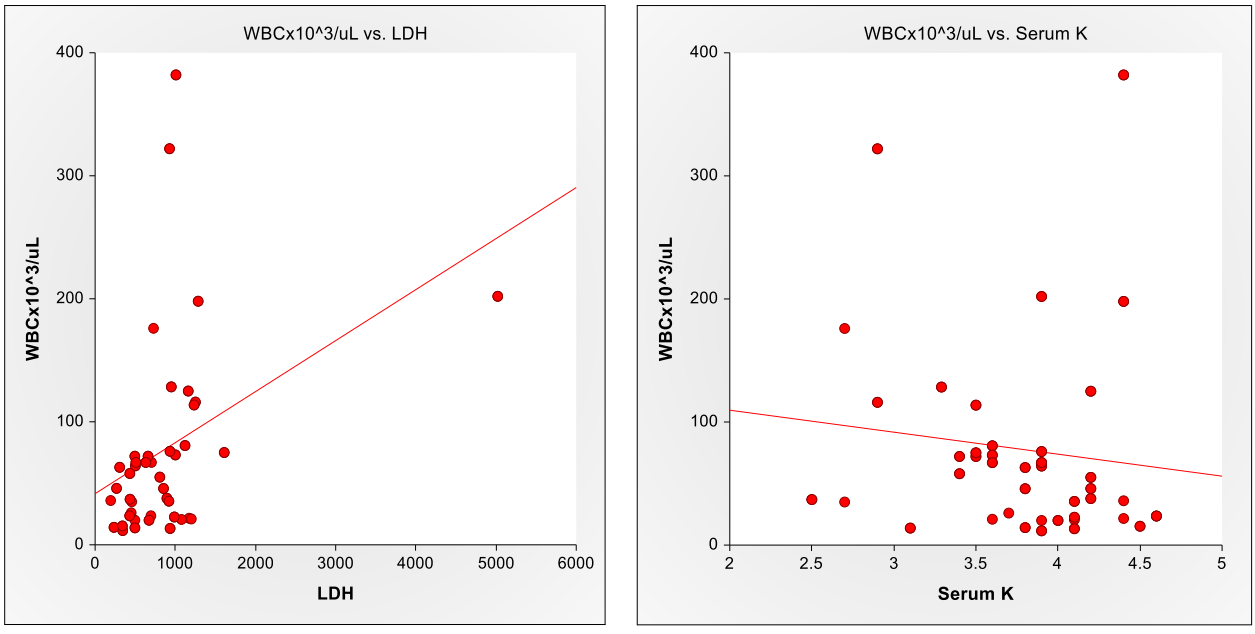

Figure (1): Linear correlation between the WBC and both LDH and Serum K in the study population

Among factors significantly correlated to white blood cell count, LDH (unstandardized β=0.03, p=0.002), peripheral blood blast cells, and serum albumin, were independently associated with it **(Table 5)**.

Table (5): Linear stepwise regression analysis of factors significantly associated with white blood cells among studied patients

Co-variates	Unstandardized Coefficients		Standardized Coefficients	t	P-value	95.0% Confidence Interval	
	β	SE	Beta			Lower	Upper
Peripheral blasts%	0.930	0.30	0.29	3.06	**0.003**	0.320	1.530
Albumin	-41.18	14.19	-0.28	-2.90	**0.005**	-69.43	-12.93
(Constant)	138.4	56.86		2.43	**0.017**	25.21	251.62

SE: Std. Error

There was a statistically significant relation between both groups and OS in favor of the control group, (the 1-year OS rate in the DEXA group was 10% vs 21% for the control, p= 0.003), as shown in **Figure 2**. On the other hand, we found a statistically non-significant relation between RFS and use of dexamethasone (the 1-year RFS rate in the DEXA group 50% vs 38% for the control, p= 0.003), as shown in **Figure 3**.

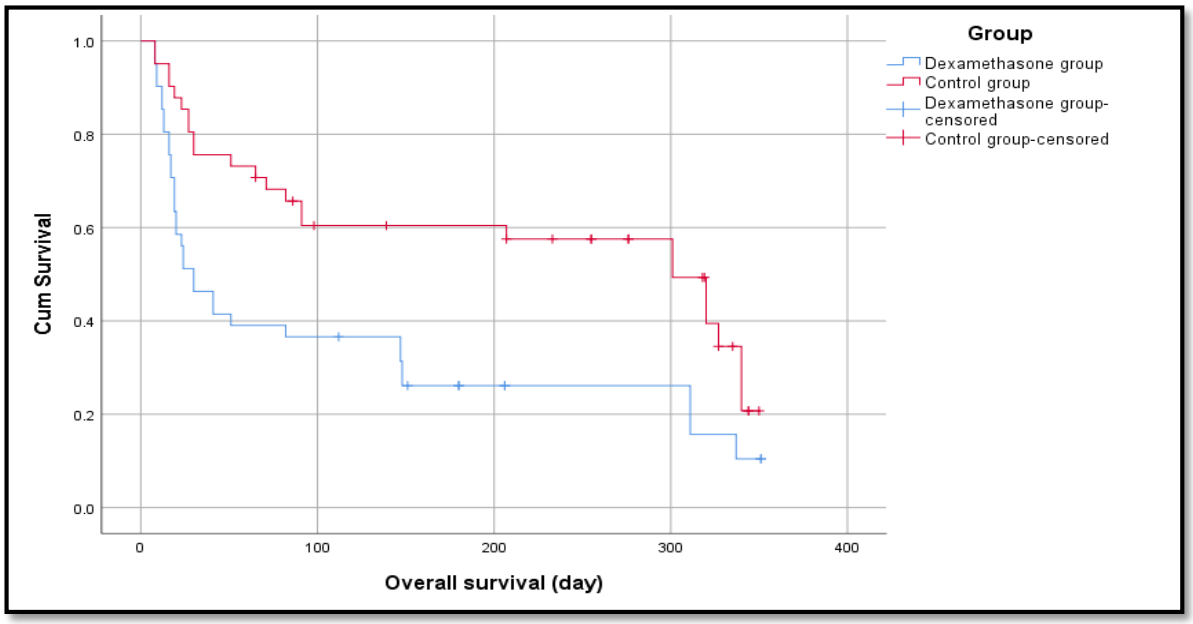

Figure (2): Kaplan-Meier plot showing relation between dexamethasone use and the overall survival rate.

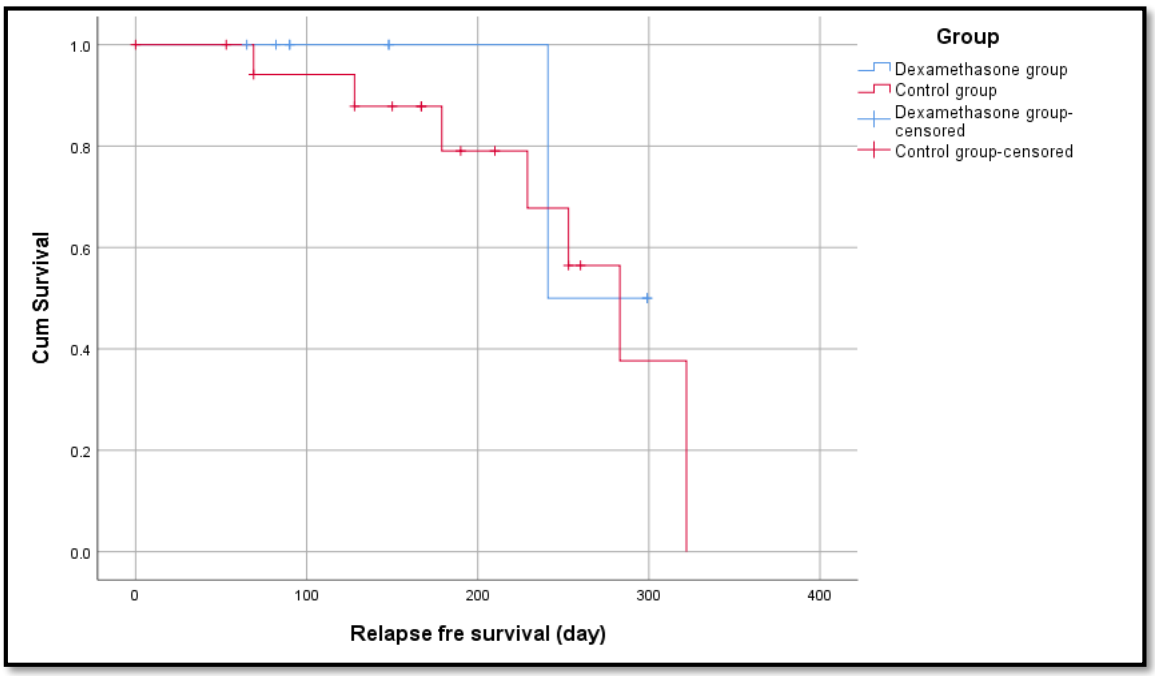

Figure (3): Kaplan-Meier plot showing relation between dexamethasone use and the relapse free survival rate

DISCUSSION

Dexamethasone has been used for a very long time to prevent or treat a severe inflammatory condition known as differentiation syndrome in adult AML patients with acute promyelocytic leukemia (APL) treated with all trans-retinoic acid (ATRA) and/or arsenic trioxide, or more recently in AML patients treated with IDH or FLT3 inhibitors [(10)].

The present study was conducted for the first time on Egyptian non-promyelocytic AML patients, aiming to improve their outcome by evaluating the effect of adding dexamethasone to induction chemotherapy on clinical and laboratory findings as well as survival in these high-risk patients with high leucocyte burden.

We conducted a randomised clinical study with 82 AML cases divided into 2 groups (41 instances in each group) in order to accomplish this goal. The first group was given an induction chemotherapy regimen of 3+7. The second group got induction chemotherapy along with dexamethasone (10 mg twice day for 3 days), according to the dexamethasone dose used in APL [(2)].

According to the baseline clinic-demographic data, our patients were relatively young as the mean age was 45.78± 13.4 years, and that is in accordance with **Sultan *et al.*** [(11)]**, Chauhan *et al.*** [(12)] and **Meng *et al.*** [(13)] who found that the mean age of the studied AML patients was 38.8, 32 and 39 years, respectively. However, this was at odds with earlier international statistics from Germany and Sweden, where the median ages were 71 and 60, respectively [(14, 15)]. The apparent geographic and genetic differences between the two populations, as well as the older average age in western nations compared to us, may help to explain this mismatch.

AML is more common in males than in women, with a male to female ratio of roughly 2:1. The current investigation's observation of a male majority (58.5% of patients) was consistent with other researches [(16,17)].

The majority of our patients (93.9%) had anemia as their primary symptom, and other symptoms included bleeding, fever, and leucostasis (24.4%, 18.3%, and 48.7%, respectively). Similar findings regarding the primary AML symptoms of bleeding, fever, and leucostasis (44.5%, 80.4%, and 30%, respectively) have been described in other AML study [(18)]. Also, **Preethi** [(19)] reported that fever and anemia were the two primary presenting symptoms (50% and 100%, respectively).

When comparing the studied groups regarding the baseline clinic-laboratory data, we found a statistically significant difference in the presence of LN swelling, fever, sepsis, calcium and uric acid (significantly higher in the control group) and that wasn't agreed by **Bertoli *et al.*** [(2)] who found a significant difference between patient groups in leucostasis, bleeding, creatinine, white blood cell and platelets count, indicating the different disease nature and clinical/biochemical aspects and confirming the heterogeneity of AML.

LDH, peripheral blood blast cells, and serum albumin were found to have a significant independent association with white blood count (p=0.002, 0.002 and 0.005, respectively), indicating that the high leucocyte burden is associated high tumor mass, malignant cellular proliferation, and acute inflammatory response.

In the present results, we found that early death occurred in 40.2%, and overall death was 69.5%. Concerning the cause of death, shock represented the most frequent cause (64.9%). Ten patients experienced relapse (40%) and complete responders represented 30.5%. 72% had PIF and 9.8% underwent bone marrow transplantation. Our results disagreed with **Erikci *et al.*** [(20)]**,** who reported that one patient developed complete response. The difference between the 2 results was possibly due to their limited number of cases (12 cases) and the different patient selection criteria as they included myelodysplastic syndrome patients.

Regarding the clinical outcome between the groups in our study, higher early death, death and 1ry induction failure rates were observed in the DEXA group (p= 0.003, 0.031 and 0.007, respectively) with lower relapse rate, (p= 0.043) and in addition there was a statistically non-significant difference between the studied groups regarding complete response rate or BMT. **Bertoli *et al.*** [(2)] were consistent with our results regarding the non-significant complete response rate or BMT, however, early death and PIF rates were not statistically significant between patient groups.

Dexamethasone has been recommended for treatment in patients with AML FAB M5 with acute lung damage or acute respiratory distress syndrome who are hospitalised to the intensive-care unit (ICU), as glucocorticoids exert a powerful inhibitory impact on cytokine production. Patients using dexamethasone saw considerably decreased death rates when compared to historical controls [(21)].

Dexamethasone medication was later demonstrated to be a factor independently related with decreased mortality on day 28 in the multivariate analysis in a trial of adult patients admitted to the ICU with respiratory problems during the initial phase of AML [(22)].

Concerning the adverse effects in our study, there was a statistically non-significant difference between the studied groups regarding the ICU admission or incidence of documented microbial infection (p = 0.137 and 0.616, respectively) and this could be due to the moderate dose/duration of Dexa used, however it may be encouraging to the use of steroids in AML because of the non-significant additive potential risk of adverse effects, and in this aspect, **Bertoli *et al.*** [(2)] reported also that there were no significant differences between the two groups (dexamethasone and without dexamethasone) in terms of fungal (P=0.710) or bacterial (P=0.192) infections. While the admissions to the ICU by day 90 were more frequent in the dexamethasone group compared to the no dexamethasone group (P<0.0001).

In the present study, there was a statistically non-significant relation between 1-year RFS and the use of dexamethasone, however, there was a statistically significant relation between both groups and 1-year OS, but unfortunately in favor of the control group, and this contrasted **Bertoli *et al.* [2],** who found that dexamethasone was significantly associated with improved disease-free survival (P=0.010), event-free survival (P<0.001), and overall survival (P=0.007), and **Farrugia *et al.* [23]** who document that the addition of dexamethasone to intensive chemotherapy results in significant better survival rates in already hyperleucocytic AML patients. This gap may be explained by their longer research period and correspondingly bigger study population, as well as by their use of various chemotherapeutic procedures and varied cut-off values for the high leucocytic count. Additionally, a number of genes, including BCL 2, FLT3-ITD, and ASXL1 mutations, play a crucial role in the response and survival of AML and should be taken into account in future study based on their prognostic significance [24, 25].

The poor effect of adding dexamethasone to induction chemotherapy in our patients could necessitate using another different dosage form as longer duration or higher concentration, taking into consideration the proper supportive care to manage the possible adverse effects.

Finally, due to the relatively small number of the studied population, we recommend further larger and multicenter studies to validate the role of dexamethasone in those risky AML patients with high leucocyte burden.

CONCLUSIONS

Our study highlighted for the first time the role of adding dexamethasone to the standard induction in Egyptian AML patients with hyperleukocytosis and revealed that; despite lowering the relapse rates, it was associated with higher treatment-related mortality and inferior overall survival with no effect on relapse-free survival.

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Competing interests: Nil.

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