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Efficacy of Low Dose Doxorubicin Therapy in Patients with Non-APL Acute Myeloblastic Leukemia

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Abstract

Background: Doxorubicin is a chemotherapeutic drug that acts by blocking topoisomerase 2 enzyme. It is used for treatment of many solid and hematological cancers; unfortunately it has serious side effects. The usual Doxorubicin dose for patients with acute myeloblastic leukemia (AML) is 40-60 mg/m^2. This is the first study that assessed the efficacy of low dose Doxorubicin in patients with non acute promyelocytic leukemia (APL) AML.

Methods: A retrospective study was done at Assiut University, where data were collected from hospital records of 103 patients with AML, after fulfilling certain inclusion criteria. Patients were treated with the conventional 3/7 induction regimen, however doxorubicin was prescribed in a lower dose compared with other studies.

Results: The median age of our patients was 38 years, and 86.4% were with primary AML. Complete remission (CR) was achieved in 60.2% of the study patients. Primary AML type and M2 FAB subtype, were found to be good prognostic factors (P=0.000 and 0.067, respectively). Survival analysis showed that the longest overall survival (OS) and disease free survival (DFS) for the study patients were 60 and 55 months respectively. There was no significant difference regarding OS and DFS between male and female patients (P=0.903, 0.848, respectively).

Conclusion: In conclusion this study provided a novel therapeutic strategy that encourages the use of low dose Doxorubicin for treatment of young age adults with non- APL AML. This will reduce treatment expenses, minimize cardiotoxicity, and allow addition of adjunctive therapy which in its turn minimizes resistance.

Keywords: Doxorubicin; Acute myeloblastic leukemia; Efficacy

Introduction

Acute myeloblastic leukemia is a blood cancer in which the bone marrow is flooded with malignant cells of myeloid lineage; these cells interfere with the growth of normal blood cells resulting in variable degrees of cytopenias [1-3] although a lot of research was conducted to develop effective targeted therapy for AML, yet the conventional 3/7 induction protocol still the gold standard for treatment of patients with AML [4-6].

Doxorubicin is a cell cycle specific anti-neoplastic drug that belonged to the anthracycline antibiotic group. Doxorubicin is used in the 3/7 induction regimen in AML, it is also used as a chemotherapy for a wide array of malignancies [7-9]. Unfortunately it can cause serious affection of the myocardium and progressive reduction of ejection fraction. This effect is mainly cumulative and could occur even 8- years after stoppage of the drug. Another serious complication of Doxorubicin is the development of secondary leukemia [10-12].

Doxorubicin is relatively the cheapest and most available anthracycline, however it is not commonly used compared to Daunorubicin and Idarorubicin. The most commonly used dose range of Doxorubicn for AML patients is 40-60 mg/m^2 [13-16].

Materials and Methods

Study objectives

This study aimed to assess the efficacy of low dose doxorubicin therapy in patients with non- APL AML.

Significance of the study

We assumed that this is the first study that assessed efficacy of low dose (25 mg/m^2) Doxorubicin in 3/7 induction regimen of patients with non-APL AML.

Study settings and design

The study was done at the Medical Oncology Department at South Egypt Cancer Institute (SECI) and the Clinical Hematology Unit at Internal Medicine Department, Assiut University Hospital (AUH). The design was retrospective that was based on hospital records of AML patients who were admitted and treated at the above mentioned Departments in the period Jan 2009- to Dec 2013. During these periods AML patients were treated with low dose Doxorubicin during induction phase of chemotherapy. Although this regimen is not commonly used, we use it in our patients due to many reasons. The most important were the cheaper price and wider availability of Doxorubicin compared to Idarubicin and Daunorubicin. Furthermore the common associated co-morbidities, low Eastern Co-operative group (ECOG) performance status of our patients and ineffective supportive measures, all of these enforced us to use lower dose Doxorubicin rather than the commonly used ones. Another important point was to reduce the possible

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incidence of cardiotoxicity when using higher doses of Doxorubicin.

Study patients

The study included AML patients who admitted and treated in the previously mentioned time and settings.

Exclusion criteria:

- Patients aged >50 years.
- Patients with M3 FAB subtype
- Patients with relapsed AML
- Patients who received therapy other than Doxorubicin such as elderly patients and those who reached the higher cumulative dose of Doxorubicin or any other anthracycline.
- Patients with incomplete hospital records

Methods of data collection

In the current study, data were collected from patients' files and hospital records, after exclusion of patients who were unsuitable for the study. Hospital records of the selected patients were thoroughly arranged and reviewed for data collection. The collected data were categorized into demographic, clinical data at presentation, hematologic parameters, French- American- British (FAB) subtype of AML, and therapeutic response. A follow up was tediously done for each patient from the date of admission to the date of death or last follow up, or relapse, or development of complications. This was mainly to estimate the overall survival (OS) and disease free survival (DFS) for each patient. During the time of the study cytogenetic and immunophenotypic analyses were not routinely done for all AML patients in our centers, accordingly these data were not available for all patients of the study, hence it was omitted.

Important definitions

The World Health Organization (WHO) criteria for AML diagnosis were applied to our patients [17]. Patients received 3/7 induction regimen in the form of Doxorubicin 25 mg/m^2/day for three days and cytarabine 100 mg/m^2/day for seven days by continuous intravenous infusion [8]. The International Working Group definition of CR was used to assess therapeutic response [17]. Accordingly CR was defined clinically by independence from RBCs transfusion and absence of any extramedullary affection, and by a peripheral hemogram that showed platelet count >100.000/ul and a neutrophil count >1000/ul. Another important criterion was absence of Auer rods and presence of <5% blast on bone marrow examination. Patients who showed suboptimal response received another cycle of induction regimen, then reassessed again, if suboptimal response persisted patients were subjected to 3rd cycle of induction and re-evaluation. Those who developed complications of the treatment or the disease were managed accordingly and their therapeutic response was included in the category of complications.

OS for patients was estimated from the first day of therapy to death. DFS for those who achieved CR was calculated from the date of CR to relapse or death.

Statistical analyses

Data were collected, coded and analyzed with SPSS V. 17.0, Inc, Chicago, USA, software for windows. Descriptive statistics of numerical variables were expressed as mean ± SD, median, minimum, maximum and range, while those of categorical variables were presented as percentages. Influence of gender, FAB subtypes, and AML type and other categorical variables on response to treatment was assessed with the Chi- square test. Spearman's Rank correlation coefficient was used to assess the association between quantitative variables and therapeutic response. Survival analysis was done using Kaplan–Meier survival analysis. Significance was considered when P value <0.05.

Ethical considerations

The study protocol and methods were in accordance with the declaration of Helsinki. Also the study design and methods were discussed and approved from the head and members of the Departments where the study was done, then was approved by the ethical committee of the postgraduate and research affairs at Faculty of Medicine, Assiut University. All of this was done before handling patients' records. Data were introduced into a personal computer and confidentiality was addressed.

Results

Characteristics of the study patients

Table 1 showed characteristics of the study patients. 103 patients

Variable	Non-APL AML patients (n=103)
Gender	
Male	57 (55.3%)
Female	46 (44.7%)
Governorate	
Assiut	65 (63.1%)
Below Assiut	20 (19.4%)
Above Assiut	18 (17.5)
Social environment	
Urban	53 (51.5%)
Rural	50 (48.5%)
Occupation	
Housewife	33 (32%)
Employed	25 (24.3%)
Farmer	24 (23.3%)
Unemployed	21 (20.4%)
Clinical characteristics symptoms	
Symptoms of cytopenias	73 (70.9%)
Symptoms of cytopenias and bone pains	21 (20.4%)
Symptoms of cytopenias and others	3 (2.9%)
Symptoms of cytopenias, bone pains and others	6 (5.9%)
Signs	
Signs of cytopenias	67 (65%)
Signs of cytopenias and HSM	24 (23.3%)
Signs of cytopenias and lymphadenopathy	7 (6.8%)
Signs of cytopenias, HSM and Lymphadenopathy	5 (4.9%)
Type of AML	
De novo	89 (86.4%)
Secondary	14 (13.6%)
Preleukemic disorder	
No	89 (86.4%)
CML	13 (12.6%)
Myelofiberosis	1 (1%)

Table 1: Characteristics of non-APL acute myeloblastic leukemia patients included in the study.

N.B. APL: Acute Promyelocytic Leukemia, HSM: Hepatosplenomegaly, CML: Chronic Myeloid Leukemia.

were enrolled in the study, their median age was 38-years, and the age range was 17-50 years. 55.3% of patients were males, and the male to female ratio was, 1.2:1. 63.1% of patients were from Assiut, 51.5% were from Urban areas. Most of the patients were farmers and unemployed (23.3% and 24.3%, respectively).

More than two thirds of patients were presented with manifestations of cytopenias. Secondary AML comprised only 13.6% of patients and chronic myeloid leukemia was the commonest pre-leukemic disorder.

Table 2, showed hematologic parameters of the study patients, in this study the median blast% was 55%. FAB subtypes of the study patients were in order of frequency FAB M2, followed by FAB M4, M1, M5, M6, M7, and lastly M1-2 (29.1% and 25.2%, 17.5%, 12.6%, 10.7%, 3.9%, and 1% respectively), as in Figure 1. Figure 2 showed distribution of the study patients over years of the study, it revealed that considerable percentage of patients were admitted during years 2011 and 2010.

Response to low dose doxorubicin therapy and fate of the study patients

60.2% of patients showed CR, from these 36.9%, 17.5%, and 5.8% showed remission after first, second and third induction respectively. A considerable proportion of our patients developed complications 21.4%, as in Table 3. It is obvious that the maximum cumulative dose of Doxorubicin in our patients was 75 mg/m^2.

Table 3, showed that nearly one third of our patients (29.1%) stopped treatment, 10.7% relapsed and 17.7% died over years of the study. 28.2% of our patients stayed in remission. In 14.4% of the study sample the fate of the patients was not available in their records.

Factors that affect response to treatment in the study patients

Table 4 showed prognostic impact of both patient and disease related factors, it revealed insignificant effect of gender on therapeutic response (P=0.47), the same was found with FAB subtypes. On the contrary a significant good prognostic impact was noted for AML type where 100% of patients who show remission after 1st induction were with de novo AML. Furthermore, 57.1% and 35.7% of those with secondary AML were either complicated or did not show remission.

The association between quantitative variables and therapeutic response was also assessed and showed a significant association

	Minimum	Maximum	Mean		SD	Skewness		Median		
	Statistic	Statistic	Statistic	Std. Error	Statistic	Statistic	Std. Error	Statistic	R	P-value
TLC	1.0	84.0	16.35	2.16	21.92	1.60	0.23	3.5	0.340**	0.000
Hb	3.0	14.4	7.02	0.20	2.09	0.36	0.23	7	-0.148	0.136
Plts	5	450	103.33	9.11	92.54	1.69	0.23	75	0.087	0.384
Blast%	22	100	58.57	2.41	24.51	0.21	0.23	55	-0.073	0.468
Age	17	50	34.70		11.53			38	0.524**	0.000

Table 2: Age and hematologic parameters of non-APL acute myeloblastic leukemia patients included in the study and their effect on the therapeutic response to Doxorubicin (n=103). N.B. TLC (x1,000/mm^3)=Total Leucocytic Count, Hb=Hemoglobin (g/dl), Plts=Platelets (x1,000/mm^3). ***Correlation is significant at the 0.01 level (2-tailed).

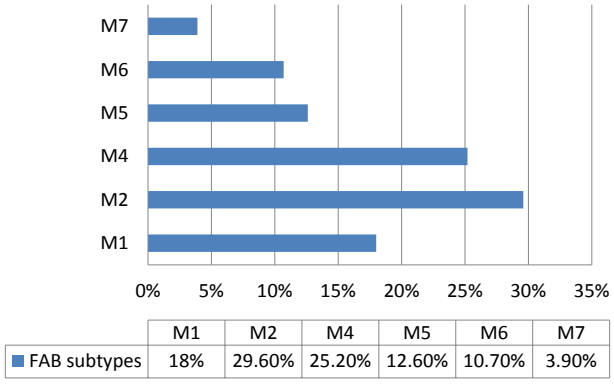

Figure 1: French-American-British (FAB) subtypes of non-APL acute myeloblastic leukemia patients included in the study (n=103).

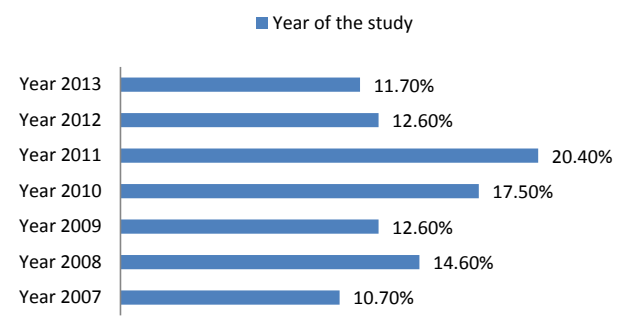

Figure 2: Distribution of non-APL acute myeloblastic leukemia patients over years of the study (from 2007 to 2013).

between age, TLC and therapeutic response, as in Table 2, however effect of other parameters was insignificant.

In Figure 3 it was clear that the best therapeutic response was obtained during the last 3-years of the study where many patients remit after 1st induction.

Survival analysis of the study patients

Kaplan Meier analysis of survival was used to assess OS and DFS of the study patients it showed no statistically significant differences in survival among male and female patients. The Mean OS was 28.9 ± 2.8 and 29.1 ± 7.6, and the mean DFS was 27.7 ± 2.6 and 29.5 ± 7.7 for male

Response	Frequency	Percent	Cumulative Percent
Not in remission	19	18.4	18.4
Complications	22	21.4	39.8
Remision after 1st induction	38	36.9	76.7
Remision after 2nd induction	18	17.5	94.2
Remission after 3rd induction	6	5.8	100.0
Fate-Relapse	11	10.7	10.7
No relapse	29	28.2	38.8
Cessation of ttt	30	29.1	68.0
Death	18	17.7	78.6
Unknown	15	14.4	100.0
Total	103	100.0	

Table 3: Response to treatment and fate of Non-APL acute myeloblastic leukemia patients (n=103).

Variable	Remision after 1st induction	Not in remission	Complications	Remision after 2nd induction	Remission after 3rd induction	P-value
Gender						
Male	23 (60.5%)	12 (63.2%)	11 (50.0%)	8 (44.4%)	3 (50%)	0.72
Female	3 (50%)	7 (36.8%)	11 (50%)	10 (55.6%)	3 (50%)	
FAB						
M1	8 (21.1%	4 (21.1%)	4 (8.2%)	2 (11.1%)	0 (0%)	
M2	13 (34.25)	3 (13.8%)	6 (27.3%)	7 (38.9%)	2 (33.3%)	
M4	7 (18.4%)	8 (42.1%)	5 (22.1%)	5 (27.8%)	1 (16.7%)	0.77
M5	6 (15.8%)	2 (10.5%)	2 (9.1%)	2 (11.1%)	1 (16.7%)	
M6	3 (7.9%	2 (10.5%)	3 (13.6%)	1 (5.6%)	2 (33.3%)	
M7	1 (2.6%)	0(0%)	2 (9.1%)	1 (5.6%)	0 (0%)	
AML type						
De novo	38(100%)	15 (78.9%)	15 (68.2%)	15 (83.3%)	6 (100%)	0.007**
Secondary	0 (0%)	4 (21.1%)	7 (31.8%)	3 (16.7%)	0 (0%)	

Table 4: X2 test results of the association between qualitative variables and response to low dose Doxorubicin therapy in patients with non-APL acute myeloblastic leukemia.

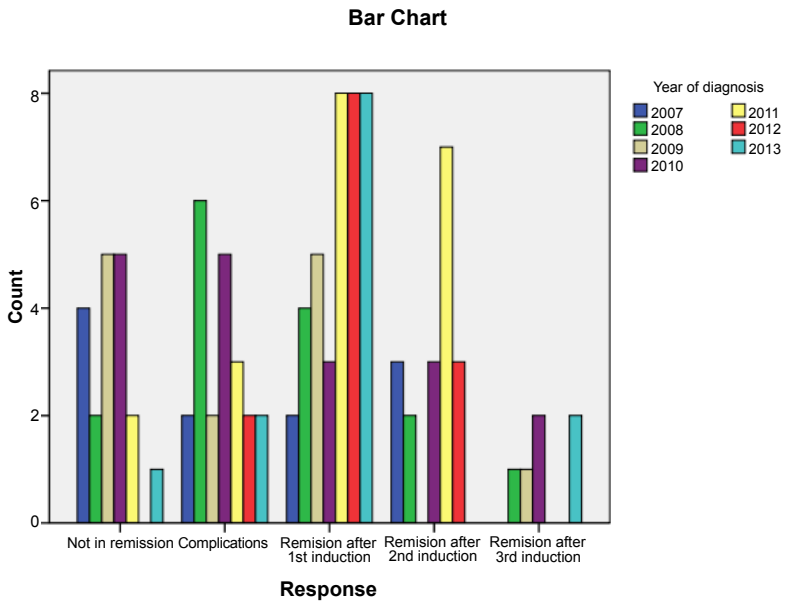

Figure 3: Bar chart of response to low dose Doxorubicin treatment in non-APL acute myeloblastic leukemia patients over years of the study.

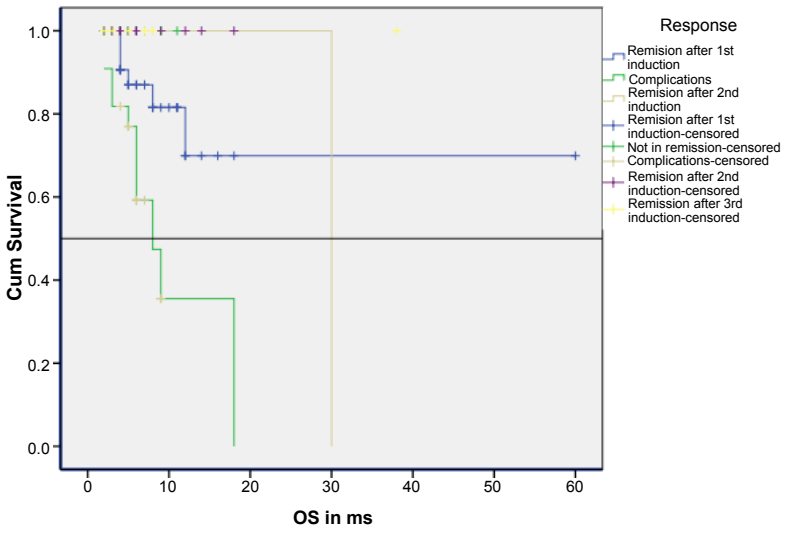

Figure 4: Kaplan-Meier survival analysis for different levels of response to low dose Doxorubicin in the study patients (Log Rank (Mantel-Cox)=22.8, P-value=000).

and female patients, respectively. The longest OS and DFS were 60 and 55 ms for the whole study group. Figure 4 illustrated overall survival of the study patients for the different levels of therapeutic response, longer overall survival was apparent for the group who remit after 1st induction.

Discussion

This study was conducted to assess the efficacy of low dose Doxorubicin in 3/7 induction regimen for patients with non- APL AML. In our center, Doxorubicin is the preferred anthracycline in induction therapy for AML compared to idarubicin or daunorubicin as it is the cheapest and most available anthracycline. It is available in 20 mg vials, and the used dose was 25 mg/m^2 (during the study years), with this dose the toxicity of the regimen is somewhat tolerable. Furthermore the possibility of exceeding the highest cumulative dose (450-550 mg/m^2) is rare for those who received recurrent inductions.

AML patients were included in this study after fulfillment of certain inclusion criteria, accordingly descriptive characteristics, concerned with gender, age, etc, of our patients could not be applied to AML patients in our locality.

In this study, induction with low dose Doxorubicin achieved 60.2% remission rate which was higher than that was achieved by Yates and his co-workers with 30 mg/m^2 Doxorubicin. In the meantime this was nearly similar to the remission rate achieved with 30 mg/m^2 Daunorubicin in the same study. These differences in response could be explained by the lack of patient selection in Yates study, accordingly the study included patients who were expected to have poor response [18].

In a recent study at the National Cancer Institute, Egypt, 45 mg/m^2 Doxorubicin in adult AML patients aged 15-60 years, achieved a CR of 67.1% [19]. This rate is nearly similar to the CR obtained in the current study. These findings confirmed the findings of Sonneveld et al., who concluded that dosage reduction may reduce toxicity with no concomitant decrease of antileukemic activity of Doxorubicin [20]. On the other hand results of our study reaffirmed the findings of many clinical trials and concluded that there is no advantage of one anthracycline over another [21].

A serious issue in treatment of AML is the development of chemoresistance, this could be in the form of primary resistance or chemoresitant relapse after achievement of CR. Resistance was found to be due to ineffective eradication of chemoresistant leukemic cells [22-24]. In this respect we suggested that our low dose Doxorubicin regimen would allow adding adjunctive treatment such as Valspodar or cladripine to avoid primary resistance or even in relapsed cases [25].

Unlike other studies, age and gender had no significant influence on therapeutic response. This is because the age range of the study patients was an inclusion criterion, thus fragile elderly patients were not included in the study. On the other hand our results supported the findings of Kayser et al., who concluded that de novo AML type is an important good prognostic factor [26-28]. Also, the current study supported other studies that showed an association between TLC, blast % at diagnosis and the obtained therapeutic responses [29,30].

A considerable proportion of our patients stopped treatment (29.1%), another group was lost during follow up (14.4%). These results was higher than other studies [27]. The main explanation of these findings is the background knowledge of Egyptian population about the poor prognosis of AML. Furthermore, most Egyptians consider chemotherapy a fatal treatment modality that worsens patient condition and shortens his life expectancy. This background image about chemotherapeutics is mainly based on the gastrointestinal, dermatological and hematological complications of chemotherapy. Accordingly lowering the dose of Doxorubicin will reduce complications and could improve this image.

Another reason for patients' incompliance is the limited availability of will equipped health centers that capable of dealing with AML patients in Upper Egypt. Accordingly patients have to travel long distances for their follow up visits. Moreover, AML create a burden on patients' families due to higher treatment expenses and lower socio-economic status of the patients.

On the other hand the death rate of our patients was lower than that in comparable studies [31]. In this study, the mortality rate included early deaths within the first 30-days and late deaths afterwards. This difference could be explained by the retrospective nature of the study that allowed considering death during hospital admission only.

Similar to other studies relapse rate in our patients was 10.7% [31]. However survival analysis of our patients was dependent in many cases on the date of last follow up and not the date of death accordingly estimation of 5-year survival was hard.

Conclusion and Recommendations

In conclusion results of this study confirmed our assumption that low dose Doxorubicin regimen is an effective, relatively cheaper and more tolerable alternative for induction of remission in young age adults with AML. Moreover the current study provided scientific evidence that recurrent induction with the same regimen in those who did not achieve CR, carries little possibility of future cardiotoxicity. Another advantage of this regimen is the safety to add adjunctive drugs and guard against resistance. However, we still need long term prospective studies to assess efficacy, safety, and advantages of this regimen.

Based on the findings of the current study we recommended low dose Doxorubicin for induction of remission in young age adults with non-APL AML.

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Conflict of Interest

The authors declared that there was no conflict of interest concerned with the study.

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