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Role of High Dose Cytarabine in Remission Induction of Acute Non Lymphocytic Leukemia (Phase III Prospective Randomized Trial)

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ABSTRACT

Introduction: Acute myeloid leukemia (AML) is a heterogeneous group of diseases characterized by uncontrolled proliferation of clonal neoplastic hematopoietic precursor cells and impaired production of normal hematopoiesis. Series of studies had established the cancer and leukemia study group B regimen of continuous infusion cytarabine 100mg/m^{2}x7 days and an anthracycline x 3 days (3 and 7 regimen) as a standard induction therapy with an overall response rate of about 60%. However, the overall survival is still disappointing.

The Aim of this Study: Is to evaluate whether the use of higher doses of cytarabine in combination with mitoxantrone in induction therapy can improve the complete remission rates and overall survival compared with the standard dose cytarabine and doxorubicin (3 and 7 regimen).

Patients and Methods: The study includes 52 previously untreated adult AML patients. Their age ranged between 16-60 years. All cases were diagnosed by complete blood count, bone marrow aspirate, cytochemistry, immunophenotyping and cytogenetics and classified according to the FAB classification system. M3 cases were excluded. Patients were randomized to group A who received standard 3 and 7 induction regimen and group B who received Cytarabine 1gm/m^2 I.V infusion over 2 hours every 12 hours for the first 3 days, and Mitoxantrone 12mg/m^2 IV infusion over 2 hours on days 3,4 and 5 (HAM regimen). Patients who achieved complete remission in both groups received a similar consolidation therapy with two cycles of cytarabine 100mg/m^2 continuous infusion over 24 hours for 5 days and doxorubicin 25mg/m^2 IV for 2 days followed by two cycles of early intensification therapy with HAM regimen.

Results: 25 patients received 3 + 7 regimen and 27 patients received HAM. Complete remission rates were similar in both groups, 17/25 patients in arm A achieved CR (68%) and 18/27 (66.7%) for patients in arm B (p=0.986). After a median follow-up period of 96 weeks, the median duration of CR was 76 weeks (mean, 70 weeks; 95% confidence interval 43-98 weeks) in patients receiving arm A versus 52 weeks (mean, 60 weeks; 95% confidence interval 41-80) for arm B (p=0.44). The mean overall survival for patients who received the 3 and 7 regimen in this study was 12 months versus 13.5 months for those received HAM. This difference didn't reach statistical significance. As regard the toxicity, HAM regimen was associated with higher incidence of mucositis (p=0.005), diarrhea (p=0.005) and more prolonged thrombocytopenia (Days with platelet count <50,000/mm^3; p=0.001).

Conclusion: Standard doses cytarabine used in induction treatment is still the gold standard for AML patients with similar efficacy and less toxicity than higher doses. The use of HAM might be deferred till the consolidation/ intensification period when the patients' tolerance becomes better.

Key Words: *High dose cytarabine – Remission induction – AML – Phase III study.*

INTRODUCTION

Acute myeloid leukemia (AML) is a heterogeneous group of diseases characterized by uncontrolled proliferation of clonal neoplastic hematopoietic precursor cells and impaired production of normal hematopoiesis leading to neutropenia, anemia, and thrombocytopenia. If untreated, patients usually die of infection or bleeding in a matter of weeks **[1]**. In the western population the overall incidence is 3.4 cases per 100 000 population; 1.2 cases per 100 000 population at age 30 and more than 20 cases per 100 000 population at age of 80 years. The median age is 20 years and has been increasing over the past decade **[2]**. Approximately 50 to 75% of adults with AML achieve complete remission (CR) with the deoxycytidine analog cytarabine and an anthracycline antibiotic, such as daunorubicin or idarubicin, or the anthracenedione mitoxantrone, which inhibit the enzyme

topoisomerase IIa. However, only 20% to 30% of patients enjoy long-term disease-free survival (DFS). The majority of patients die of their disease, primarily because of persistent or relapsed AML **[3]**. In an Eastern Cooperative Oncology Group (ECOG) analysis of the outcome of approximately 3000 patients with previously untreated AML entered on 5 successive clinical trials with cytarabine and daunorubicin for induction and with increasingly more intensive post remission therapy, 62% achieved CR, but 76% relapsed or died. The 5-year overall survival (OS) rate among 2000 patients younger than 55 years has improved from 11% in the 1970s to 37% in the 1990s **[4-6]**. The outcome for adults with AML depends on a variety of factors, including age of the patient, intensity of post-remission therapy, and biologic characteristics of the disease, the most important of which are the cytogenetics at presentation **[7-9]**. Other factors include the overexpression of transmembrane transporter proteins, which extrude certain chemotherapeutic agents from the cell and confer multidrug resistance, and mutations in or overexpression of specific genes such as CEBPA, BAX and the ratio of BCL2 to BAX, BAALC, EVI1, KIT, and FLT3 **[10-14]**.

During the past 35 years, a series of studies had established an induction regimen of the cell cycle-specific agent cytarabine 100mg/m^2 by continuous I.V infusion for 7 days and an anthracycline to become the standard of care for patients not participating in a clinical Trial **[15-16]**.

To improve the CR rates, studies have tested alternative and higher doses of anthracyclines or the anthracenediones **[17-20]**, higher doses of cytarabine **[21-23]**, new agents combined with cytarabine and/or daunorubicin such as etoposide, the purine analog fludarabine or the camptothecin topotecan **[24-26]** or sequential standard therapy followed by high doses of cytarabine **[27-28]**. Despite theoretic advantages, none of these approaches is definitively better than the standard regimen. Various strategies have been explored to eliminate minimal residual disease not apparent in the bone marrow of patients in CR which could contribute to relapse. Such strategies have included intensive consolidation therapy, high-dose chemotherapy, or chemo radiotherapy with either allogeneic or autologous hematopoietic stem-cell transplantation (HSCT), or low-dose maintenance therapy **[3]**. Although post remission therapy is a sine qua non for curing AML, fundamental issues remain unresolved. The optimal dose, schedule, and number of cycles of consolidation chemotherapy for most patients with AML who achieve CR have not been established. In younger patients, cycles of intensive consolidation chemotherapy, often with, but not limited to, high-doses of cytarabine, prolong DFS and OS **[20]**.

This study was planned to evaluate whether the use of higher doses of cytarabine in combination with mitoxantrone in induction therapy can improve the remission rate and overall survival compared with the standard dose cytarabine and doxorubicin (3 and 7 regimen). Correlation of clinical and biological factors which might affect response rate and survival were also studied.

PATIENTS AND METHODS

Fifty two patients, age 16-60Y, with previously untreated AML, presenting to the NCI in the period between October 2000 and December 2002 were included in this study. Patients with acute promyelocytic leukemia (M3), secondary leukemia, previous chemotherapy, CNS involvement, Prior history or clinical evidence of congestive heart failure, unstable angina, myocardial infarction or Performance status >3 were excluded.

Pretreatment evaluation included:

1- History and physical examination.

2- Complete blood count with differential and platelet counts.

3- Bone marrow smears stained with Romanovesky stain for bone marrow cellularity and percentage of blasts.

4- *Cytochemistry:* Myeloperoxidase (or Sudden Black) supplemented by Periodic acid shiff, acid phosphatase; acid esterase and non-specific esterase when necessary.

All cases were classified according to the French, American, British (FAB) classification.

5- *Immunophenotyping:* Immunophenotyping on peripheral blood and bone marrow samples was done at diagnosis using flow cytometry to detect the phenotype.

6- *Cytogenetic analysis:* Done on bone marrow samples for chromosomal study.

7- Serum chemistry including hepatic and renal profiles, tumor lysis panel including serum sodium, potassium, magnesium, calcium phosphorus and uric acid during therapy.

8- *Multiple drug resistant gene detection: Indirect staining:* 100µl whole blood were lysed using lysis solution (Becton and Dickenson) for 10 minutes cells were washed once in phosphate buffered saline (PBS), resuspended in 100 (l. CD_4 E_3 moAb (DaKo) added and incubated for 10 minutes at 4ºC. 10µl of secondary antibody (antimouse IgGFITC) was added for 30 minutes. The cells were washed twice in PBS, suspended in 500µl and analyzed on the flow cytometry.

9- Base line chest X-ray, abdominal ultrasonography, echocardiography and ECG. Computer tomography (CT) was done if clinical situation arises.

Treatment plan:

Remission induction:

Patients were randomized into two arms *Arm A: Received the conventional 3 and 7 regimen consisting of Cytarabine 100mg/m^2 I.V continuous infusion over 24 hours for 7 days, and doxorubicin 25mg/m^2 intravenous (IV) shot for 3 days. *Arm B: Received Cytarabine 1gm/m^2 IV infusion over 2 hours every 12 hours for the first 3 days, and Mitoxantrone 12mg/m^2 IV infusion over 2 hours on days 3,4,5. Bone Marrow aspirate (BMA) was done on Day 14. Partial remission or stationary disease by BM aspirate on day 14 warranted a second induction with the same regimen.

Consolidation therapy:

Patients who achieved complete remission received consolidation therapy consisting of: 2 cycles of Cytarabine 100mg/m^2 continuous I.V infusion over 24 hours for 5 days and doxorubicin 25mg/m^2 IV shots for 2 days followed 3-4 weeks later by two cycles of Cytarabine 1gm/m^2 IV infusion over 2 hours every 12 hours for the first 3 days and Mitoxontrone 12mg/m^2 IV infusion over 2 hours on days 3, 4, 5. Patients who achieved complete remission and were eligible for bone marrow transplantation were referred for Allogenic BMT. Toxicity and adverse effects were reported according to WHO criteria. Response rate was reported according to CALGB response criteria **[16]**.

Statistical analysis:

Statistical analysis was done using IBM compatible computer and according to the following tests.

-Statistical tests:

Descriptive statistics was presented in frequency tables, means, and standard deviations whenever appropriate.

-Analytical tests used included:

- Chi-square test for comparing two quantitative variables. Comparison of means of two groups is done by student's *t*-test for unpaired series and by Paired *t*-test when a subject is taken as his own control.
- Survival analysis and analysis of duration of complete remission were done using Kaplan Meier analysis.
- Correlation between quantitative variables is done by the *r*-test diagrammatically represented by scatter dot diagram.

Significance level of 0.05 was used in all statistical tests.

RESULTS

I- *Patient Characteristics:*

A total of 52 patients were included in this study. Twenty five patients in arm A and 27 patients in arm B. The study included 22 females (42.3%) and 30 males (57.7%) with homogenous distribution of patient characteristics between both arms (Table 1). The mean age in arm A was 27.4±9.46 and in arm B was 31.12±10.45. At the time of diagnosis 40.4% of patients had a total leucocytic count below 25x10^9/L compared to 34.6% and 25% for those who had TLC between 25-100x10^9/L and 100x10^9/L respectively. Hemoglobin level more than 8mg/dL was encountered in 36.5% of patients, and 63.5% had a hemoglobin level below 8mg/dL. 61.5% of patients had a platelet count more than 25x10^9/L compared to 38.5% having a platelet count less than 25 x 10^9/L. The mean percentage of blasts in marrow was 65.5±19.9 and 59.9±25 in group A and B respectively. In group A: The most commonly encountered FAB subgroup was M1 (40%), followed by M2 (28%) while in group B: M1 and M2 were equally

encountered in (33.3%) of cases. Chromosomal analysis was obtained in 24 patients (Table 2). Fifteen cases (62.5%) showed karyotypic abnormalities. Numerical abnormalities were encountered in 6 cases: Hyperploidy in 3 cases and hypoploidy in 2 cases. Structural abnormalities were encountered in 10 cases. Only one case showed concomitant numerical abnormality. The expression of MDR-1 gene was tested in 37 patients, 23 found to be positive (62.2%) and 14 (37.8%) were negative.

II- *Response rate, duration of response and overall survival:*

Complete response (CR):

Complete remission was achieved in 35 out of 52 patients (67.3%). Among those who received arm A, 17/25 achieved CR (68%) compared to 18/27 (66.7%) among those who received arm B. The difference was not statistically significant (p=0.986) Table (3).

Early death:

Early death was encountered in 6 out of 25 patients (24%) of patients of group A, while in group B, 7 out of 27 patients died early (25.9%). The difference was not statistically significant (p=0.986). Septicemia (39%) was the leading cause of death in our patients followed by cerebral hemorrhage (21%).

Duration of complete remission:

After a follow-up period of 96 weeks the median duration of CR was 76 weeks with a mean duration of 70 weeks (17.6m) (95% confidence interval 43-98 weeks) in patients receiving arm A treatment. As for patients receiving arm B the median duration of CR was 52 weeks with a mean of 60 weeks (15m) (95% confidence interval 41-80 week). No statistically significant difference was noticed between the tow groups Fig. (1).

Overall survival:

The median overall survival for patients receiving SDAC in this study was 12 months versus 13.5 months for those receiving HDAC this difference does not reach statistical significance. The number of cases surviving at 48 weeks were 10 cases (40%) in arm A and 14 (56%) in arm B, while at 96 weeks it was 5 (20%) cases in arm A and 3 (12%) in arm B Fig. (2).

Analysis of important prognostic factors among all patients revealed that none of the factors listed in Table (4) showed statistically significant influence on complete remission except the pretreatment total leucocytic count. There was statistical significant difference in CR between patients with leucocytic counts <25,000/mm^3 compared to patients with higher counts. The only prognostic factor that impacted the DFS and OS was performance status (PS). Patients with PS I (ECOG) at presentation showed statistically significant longer duration of complete remission and significant improvement of survival as shown in Tables (4-6).

III- *Toxicity:*

Scoring of treatment toxicity was done according to WHO criteria. Alopecia was observed in 21 patients (40.4%) grade I in 11 (21.2%) patients and grade II in 10 (19.2%) patients. The difference between group A and B was not statistically significant (p=0.1). Mucositis was encountered in 69.2% of patients. Grade I in 11 patients (21.2%), grade II in 19 patients (36.5%) and grade III in 6 patients (11.5%). The incidence and severity of mucositis were significantly higher in group B compared with group A (p=0.005). Twenty nine (55.8%) patients developed nausea and vomiting, grade I in 38.5% and grade II in 17.3% of patients. Although the incidence and severity were higher in group B rather than group A, yet the difference did not reach statistical significance (p=0.2). Diarrhea was observed in 24.4% of all cases, grade I in 22.2%, and grade III in 2.2% of patients. According to the type of regimen, higher incidence of diarrhea was observed in those who received arm B (53.3%) compared with 10% among the group of patients who received arm A and the difference was highly significant (p=0.005). Cholestatic jaundice developed in 3 (12%) patients receiving arm A and also in 3 (11.1%) receiving arm B. Table (7).

Hematological toxicity: The maximum nadir was reached after a mean of 15.48±2.46 days in arm A and 15.9±3 days in arm B. The difference was not statistically significant (p=0.5). The mean duration of neutropenia (neutrophils <500 mm^3) was (8.24±5.166) days in arm A, compared with (7.17±5.122) days in arm B. The difference was not significant (p=0.4). Also there was no statistical significant difference

in the mean duration of neutrophilic counts between 500-1000/mm^3 in both groups being 6.29±3.37 and 6.46±3.82 days for those who received arm A and arm B respectively (p=0.8). An attempt was done to correlate the duration of neutropenia less than 500x10^9/L and days of antibiotic and antifungal treatment, no significant impact was found. p value was (0.5) and (0.618) for days on antibiotic and antifungal therapy respectively. The mean duration of platelet count less than 50x10^9/L was 18±4.95 and 21±5.12 in arm A and B respectively. The difference reaches statistical significance (p=0.001). (Table 8; Figs. 3,4).

Table (1): Patient characteristics of both groups.

		Arm A (n=25)	Arm B (n=27)	p-value
Age (years)	<25	11 (44%)	9 (33.3%)	0.63
	25-45	11 (44%)	14 (51.8%)	
	>45	3 (12%)	4 (14.8%)	
Sex	Female	10 (40%)	12 (44.4%)	0.74
	Male	15 (60%)	15 (55.6%)	
PS (ECOG)*	I	13 (52%)	16 (59.25%)	0.36
	II	9 (36%)	8 (29.6%)	
	III	3 (12%)	3 (11.11%)	
TLC(x10^9/L)**	<25	9 (36%)	12 (44.4%)	0.8
	25-100	9 (36%)	9 (33.3%)	
	>100	7 (28%)	6 (22.2%)	
% of leukemic cells in BM	<50	5 (20%)	12 (44.4%)	0.06
	≥50	20 (80%)	15 (55.6%)	
CD34	+ve	10 (40%)	11 (40.7%)	0.87
	–ve	9 (36%)	11 (40.7%)	
	Not done	6 (24%)	5 (18.5%)	
MDR***	+ve	9 (36%)	14 (51.85%)	0.286
	–ve	8 (32%)	6 (22.22%)	
	Not done	8 (32%)	7 (25.92%)	
FAB****	M0	1 (4%)	0 (0%)	
	M1	10 (40%)	9 (33.3%)	0.5
	M2	7 (28%)	9 (33.3%)	
	M4	5 (20%)	4 (14.8%)	
	M5	2 (8%)	2 (7.4%)	
	M5b	0	3 (11.1%)	
Cytogenetics	Favorable	9 (36%)	5 (18.5%)	0.56
	Unfavorable	3 (12%)	7 (25.9%)	
	Not done	13 (52%)	15 (55.5)	

*PS: Performance Status (Eastern Cooperative Oncology Group).
**TLC: Total Leucocytic Count.
***MDR: Multiple Drug Resistance.
****FAB: French, American, British Classification System.

Table (2): Chromosomal analysis in all patients.

No. of studied cases	Chromosomal of analysis
5	46xy
4	46xx
4	t (8;21)
3	47xy, +8
1	45xx,-7
1	46xy,10q-
1	46xy,11q+
1	12q-,-17
1	Del 12q
1	Inv 16
1	45xy,-7
1	t (9;22), 7q-

Table (3): Overall response rate in both regimens.

	Arm A	Arm B	p-value
Complete response	17 (68%)	18 (66.7%)	0.986
No response	2 (8%)	2 (7.4%)	
Early death	6 (24%)	7 (25.9%)	
Total	25	27	

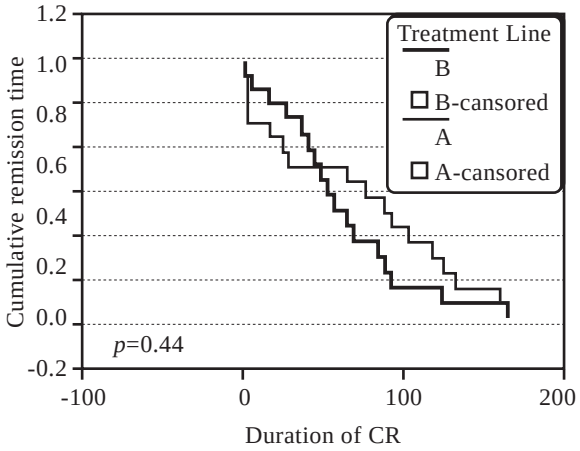

Fig. (1): Duration of remission according to type of regimen.

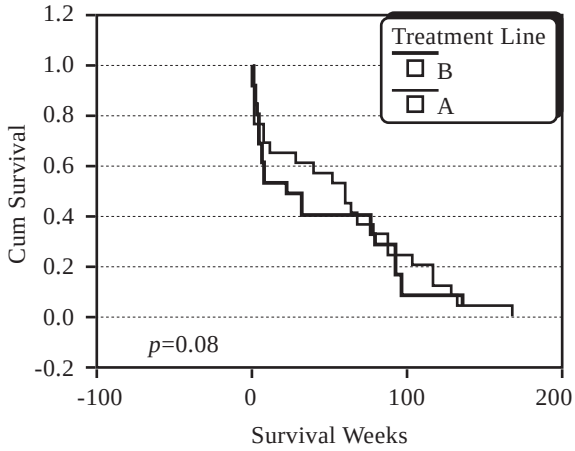

Fig. (2): Overall Survival according to type of regimen.

Table (4): Factors affecting complete remission rate.

Parameter	Complete remission	*p* value
Age (years):		
>25	15/19 (78.94%)	
25-45	15/27 (55.55%)	0.7
>45	2/6 (33.33%)	
PS (ECOG):		
I	20/30 (66.66%)	
II	12/19 (63.15%)	0.8
III	1/1 (100%)	
TLC ($X10^9$/L):		
<25	16/16 (100%)	
25-100	13/19 (68.42%)	0.03
>100	6/17 (35.29%)	
% of blasts in BM:		
<50	20/22 (90.9%)	
≥50	20/30 (66.66%)	0.7
FAB:		
Favorable (M1, M2)	25/31 (80.64%)	
Others	10/17 (58.82%)	0.2
MDR:		
+ve	13/23 (56.52%)	0.9
–ve	9/18 (50%)	
Cytogenetics:		
Favorable	10/14 (71.42%)	
Unfavorable	8/10 (80%)	0.5
CD34:		
+ve	15/21 (71.42%)	
–ve	10/21 (47.61%)	0.3

Table (5): Factors affecting duration of complete remission.

Parameter	Mean duration of CR (weeks)	95% confidence interval	Significance
PS (ECOG):			
I	79	(58,99)	Significant
II	31	(9,53)	(p<0.05)
III	68	(68,68)	
TLC ($X10^9$/L):			
<25	73	(50,95)	0.1
25-100	63	(32,95)	
>100	51	(11,92)	
FAB:			
Favorable (M1 & M2)	72	(51,93)	0.2
Others	50	(27,73)	
CD34:			
+ve	72	(45,98)	0.6
–ve	84	(52,116)	
MDR:			
+ve	77	(53,102)	0.7
–ve	73	(37,109)	
Cytogenetics:			
Favorable	83	(46-120)	0.4
Unfavorable	58	(32-84)	

Table (6): Factors affecting survival.

Parameter	Mean duration of CR (weeks)	95% confidence interval	Significance
PS (ECOG):			
I	65	(47,83)	
II	27	(9,45)	Significant
III	33	(0,94)	(p<0.05)
TLC ($X10^9$/L):			
<25	68	(45,90)	Not significant
25-100	51	(28,74)	
>100	29	(5,52)	
FAB:			
Favorable (M1, M2)	56	(38,74)	Not significant
Others	41	(21,61)	
CD34:			
+ve	57	(36,78)	Not significant
–ve	48	(22,74)	
MDR:			
+ve	49	(28,70)	Not significant
–ve	53	(22,84)	
Cytogenetics:			
Favorable	64	(36,93)	Not significant
Unfavorable	54	(26,82)	

Table (7): Non Hematological toxicity encountered in both groups of patients.

Toxicity	G0 No. (%)	G1 No. (%)	G2 No. (%)	G3 No. (%)	G4 No. (%)	p-value
Alopecia:						
Arm A	14 (56%)	8 (32%)	3 (12%)	0	0	0.129
Arm B	17 (63%)	3 (11.1%)	7 (25.9%)	0	0	
Mucositis:						
Arm A	13 (52%)	5 (20%)	4 (16%)	3 (12%)	0	0.005
Arm B	3 (11.1%)	6 (22.2%)	15 (55.6%)	3 (11.1%)	0	
Nausea/vomiting:						
Arm A	14 (56%)	8 (32%)	3 (12%)	0	0	0.245
Arm B	9 (33.3%)	12 (44.4%)	6 (22.2%)	0	0	
Diarrhea:						
Arm A	22 (90%)	3 (10%)	0	0	0	0.005
Arm B	13 (46.7%)	13 (46.7%)	0	1 (6.6%)	0	
Hepatobiliry:						
Arm A	22 (88%)	2 (8%)	0	1 (4%)	0	0.26
Arm B	24 (88.9%)	0	2 (7.4%)	1 (3.7%)	0	

Table (8): Hematological toxicity in both groups.

	Arm A	Arm B	p-value
Mean duration of days neutrophils <500 x 10^9/l	8.24±5.16	7.17±5.12	0.489
Mean duration of days neutrophils 500-1000 x 10^9/l	6.29±3.37	6.46±3.82	0.874
Mean duration of days platelet count ≤50 x 10^9/l	18±4.95	21±5.12	0.001

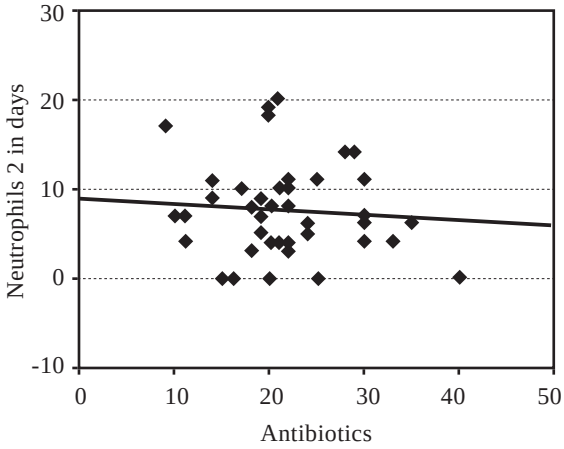

Fig. (3): Correlation between duration of neutropenia less than 500 in days and duration of antibiotic in days.

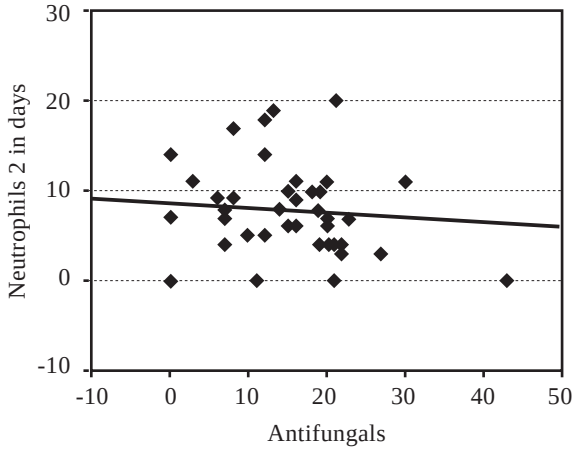

Fig. (4): Correlation between duration of neutropenia less than 500 in days and days of antifungal treatment.

DISCUSSION

The standard induction treatment of AML was established nearly 20 years ago with a combination of SDAC at 100mg/m^2/d plus 3 days of anthracyclines, either doxorubicin or DNR. Higher doses of cytarabine have been evaluated for induction therapy in AML since 1979 **[3]**.

The effectiveness of HDAC is presumed to be a result of higher intracellular concentration of cytarabine **[29]**. Uncontrolled studies have been reported using doses of 1.5 to 3g/m^2 every 12 hours for 4 to 6 days, with CR rates as high as 90% **[30-31]**. The small size and uncontrolled nature of these studies leaves some doubt about their significance.

This study included 52 patients diagnosed with AML. Patients were randomized into two treatment arms for induction. Arm A received the conventional 3 & 7 and arm B received HDAC and Mitoxontrone. Complete remission rates were similar between SDAC (68%) versus HDAC (66.7%). No statistically significant difference was noticed in duration of CR between the two treatment arms in this study (The median duration of CR was 17.6 and 15 months for SDAC arm and HDAC arm respectively). The median overall survival for patients receiving SDAC in this study was 12 months versus 13.5 months for those receiving HDAC this difference does not reach statistical significance.

Our results partially comply with previous studies. Bishop et al., 1996 **[21]**, randomized 300 patients with AML for induction with HDAC as 3gm/m^2 for 8 doses together with anthracycline and etoposide compared with SDAC with anthracycline and etoposide and reported similar response rates but longer duration of CR in the HDAC arm. However, there was no significant difference in overall survival. The only prognostic factors that were associated with improved incidence and duration of CR rates were performance status I (ECOG) and WBCs less than 25x10^9/L at presentation. The same findings were reported by Weick et al., 1996 **[22]**, who reported similar results. The HDAC arm was associated with higher toxicity and mortality. This is recently reconfirmed by Kern and Estey, 2006 **[32]** in their meta-analysis of randomized controlled trials which test induction with HDAC compared with SDAC and reported equal response rate and survival with longer DFS in the HDAC arm.

Furthermore in our study, patients who receive HDAC in the induction and consequently in the consolidation/early intensification therapy, did not show any change in the DFS or overall survival compared with the group who received HDAC in the consolidation/early intensification following SDAC in the induction therapy. This is in agreement with Bradstock et al., 2005 **[33]** who showed that Intensive induction chemotherapy incorporating high-dose cytarabine results in high complete remission rates, but further intensive consolidation treatment does not appear to confer additional benefit. However, it is different from the results of Weick et al., 1996 **[22]**, who reported improvement of survival with intensive post remission therapy.

Comparison of the of toxicity profile between the two treatment arms showed a statistically significant higher incidence of Mucositis and diarrhea in patients receiving HAM. Whereas the incidence of alopecia, nausea, vomiting and hepatobiliary toxicities were comparable in both groups. Similar results were reported by the previous studies **[22,32,33]**. The mean duration of neutropenia and requirement of systemic antibiotic and antifungal among patients who received SDAC and HDAC showed no statistically significant difference. Bishop et al., 1996 **[21]** reported no difference in the duration of severe neutropenia (neutrophils less than $0.5x10^9/L$). In their study there was statistically significant increase in the number of days of antibiotic use and in the organisms isolated by cultures. CNS toxicity was not encountered in any of our patients whether arm A or arm B. Mortality during induction was higher in the high dose Ara-c arm which is in agreement with the previous 2 studies **[22,32]**.

Although this study showed partial agreement with previous and current studies, yet we there was no DFS benefit in the HDAC arm. This could be multifactorial due to better disease biology in the SDAC arm compared with HDAC (more favorable Cytogenetics and less MDR-1 expression) or due to treatment effect. Also, the dose of Ara-c used in this study is lower than those used in previously mentioned studies both in induction and consolidation. Actually, Ara-c is a schedule dependent chemotherapeutic agent and the dose of $1gm/m^2$ might not be much different form $100mg/m^2$ given by continuous infusion. Etoposide was used as part of the induction treatment regimen in some studies which could have impacted their duration of DFS.

Also, the fact that the total group incidence of MDR expression in our patients was high (62%), despite of all being newly diagnosed patients compared to Del Poeta et al., 1994 **[34]** who reported a 20% positivity in de novo AML cases. Furthermore, the smaller number of our patients and the single institute nature of the study might have affected the results. In conclusion, HDAC failed to show improvement of response rates, DFS or OS and was associated with higher toxicity and mortality. Accordingly, SDAC induction treatment is still the gold standard for AML induction. The use of HDAC might be deferred till the consolidation period when the patient tolerance becomes better.

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