

The Prevalance of Sensori-Neural Hearing Loss and Ototoxicity in Acute Myeloid Leukemia Patients

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Abstract

Objective: The aim of this study is to investigate the prevalence of sensori-neural hearing loss and ototoxicity in acute myeloid leukemia (AML) patients.

Study design: This is a prospective non-randomized study.

Methods: 14 patients with the diagnosis of acute myeloid leukemia were treated with Daunorubicin and Cytarabine (ARA-C). Pure Tone Audiometry (PTA) was performed prior to induction chemotherapy and immediately after completion of induction protocol. Primary outcome was the prevalence of sensori-neural hearing loss. Secondary outcome was correlation of age, sex, absolute neutrophil counts, total white counts, platelet counts and creatinine levels in the study population.

Results: Fourteen patients participated in this study (n=14). Ten patients had normal hearing prior to pre-induction treatment. Four patients had pre-existing hearing loss prior to treatment. Post induction treatment, ten patients had normal hearing. However, from these ten patients, one had pre-existing hearing loss which improved. Two patients, whom had normal hearing and pre-existing hearing loss pre-induction treatment respectively, expired. Two patients who had pre-existing hearing loss had the same level of hearing post induction. The prevalence of sensori-neural hearing loss in this study is 71.4%. From our observation, there is no evidence of ototoxicity from induction therapy of Daunorubicin and Cytarabine (ARA-C) in our study population (p=0.001). Induction treatment with Daunorubicin and Cytarabine (ARA-C) shows statistically significant reduction in Absolute Neutrophils Counts (p=0.013), Total White Counts (p=0.001), Haemoglobin Counts (p=0.036) and Creatinine levels (p=0.017) in our study population. Even though Platelet counts showed reduction, this was not supported statistically (p=0.258).

Conclusion: Induction treatment with Daunorubicin and Cytarabine (ARA-C) are safe chemotherapy agents to be administered during the induction phase in treatment of Acute Myeloid Leukemia with no evidence of sensori-neural hearing loss. Further study is required to monitor the long-term effects of these drugs during consolidation, remission or relapse phases of treatment and if possible during stem cell transplant treatment.

Keywords: Sensori-neural hearing loss; Acute myeloid leukemia; Ototoxicity

Introduction

Standard induction protocols in treatment of acute myeloid leukemia (AML) comprise treatment of anthracycline and anthracenedione administration. Commonest anthracycline and anthracenedione administered are Daunorubicin and Cytarabine (ARA-C). Anthracyclines inhibit Deoxyribonucleic Acid (DNA) and Ribonucleic Acid (RNA) synthesis by intercalating the DNA and RNA strands thereby preventing replicating of rapidly growing cancer cells. Anthracenedione is an anti-metabolite and holds the cells in the S-Phase of cell cycle. It also inhibits the DNA and RNA polymerases enzymes which are required for DNA synthesis. Prior to this, there are no attributes of side effects of Acute Myeloid Leukemia chemotherapy agents in induction phase causing sensorineural hearing loss. [1,2]. The occurrence of hearing loss in short duration administration (i.e., induction phase) has not been reported in the past [3].

Anthracyclines present a risk of both early and late cardiotoxicity owing to selective toxicity of myocardial tissue, with a progressive dose-dependent dilated cardiomyopathy that irreversibly evolves toward congestive heart failure [4,5].

Cytarabine can cause both peripheral and central nervous system toxicities [6,7]. Most concerning is cerebellar dysfunction consisting of dysarthria, ataxia and possible confusion or lethargy. There is usually

complete resolution of symptoms within two weeks of discontinuing the drug, but some patients suffer permanent impairment. Peripheral nervous system toxicity is uncommon, but peripheral neuropathies and brachial plexopathy have been described.

Treatment of AML with Daunorubicin and Cytarabine (ARA-C) as induction protocols offer the initial remission and overall survival. Kaspers et al. analyzed data from 13 original manuscripts of centers in AML therapy. Therapy constitutes of intensive courses of chemotherapy based on cytarabine and an anthracycline achieved mainly complete remission with reduced side effects and high-quality cure [8].

In another study, the usage of these chemotherapy agents in treatment of AML with current guidelines make results of clinical trials and adverse effects more comparable and interpretable [9].

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These patients are then further subjected to consolidation protocols and depending on partial response, complete response or refractory to treatment, other chemotherapy agents are commenced.

Specific ototoxicity of the chemotherapeutics used in AML has not been described and hearing loss after treatment for AML is likely related to the frequent use of aminoglycosides during neutropenic sepsis [5].

Thus, we wish to embark on the study to analyse the prevalence of sensorineural hearing loss in Acute Myeloid Leukemia patients.

Objectives

To assess the prevalence of sensorineural hearing loss in acute myeloid leukemia patients.

To describe the significance of age, sex, absolute neutrophil counts, total white counts, Haemoglobin counts, platelet counts and creatinine levels in the study population of acute myeloid leukemia patients.

To intervene if treatment from acute myeloid leukemia induced ototoxicity occurs in the absence of usage of aminoglycosides.

Methods and Materials

Study design

This is a prospective non-randomized study to assess the prevalence of sensorineural hearing loss in selected acute myeloid leukemia patients at the Haematology Unit, Medical Department, Ampang Hospital, Ampang, Malaysia from December 2015 to December 2016. This study was approved by the Medical Ethics Committee, University Malaya Medical Center (MECID number: 20156-1386) and National Medical Research Register (NMRR number: 26572).

Patients

Patients were carefully selected from the Haematology Unit, Medical Department, Ampang Hospital. A total of 14 patients were selected during the mentioned study time. All these patients were diagnosed with Acute Myeloid Leukemia. Inclusions criteria were Acute Myeloid Leukemia patients prior to treatment initiation. Exclusion criteria were age less than 12 years old and more than 60 years old; external ear and middle ear pathology. All patients underwent demographic screenings and investigations of base line full blood count/differential count and renal profile were taken. Disease stratification of acute myeloid leukemia was done as per the unit's protocol. Examination of the ears was done using otoscope. Tuning fork tests of Rinne and Weber's test (512 Hz) was performed. A Pure Tone Audiometry was done prior to induction treatment initiation and post-induction treatment completion. Induction treatment comprises of 3 days of Daunorubicin (Day 1-3) and 7 days of Cytarabine (Day 1-7).

All patients were consented and were given a patient information sheet prior to enrolment into the study.

Outcome measures

The outcome measures were divided into primary and secondary. Primary outcome was the prevalence of sensori-neural hearing loss. Secondary outcome was correlation of age, sex, absolute neutrophil counts, total white counts and creatinine in the study population. The above measures were taken pre and post induction treatment.

Pure tone audiometry

Pure Tone Audiometry was done using Interacoustic Audiometer AC 40. This was able to pick up sound frequency ranging 0.25 to 16kHz.

Statistical analysis

The Statistical Package for the Social Sciences version 23 (IBM SPSS Statistics 23) and the Microsoft Excel Office Professional Plus 2010 were utilized for statistical analysis. The baseline demographic data were expressed as mean and standard deviation for continuous data or frequency and percentages for categorical data. The correlation between values obtained pre and post induction chemotherapy were analyzed with Chi-Square Tests and paired with Pearson Chi-Square, Likelihood Ratio and Linear-By-Linear Association. A value of $p < 0.05$ was considered significant. Wilcoxon Signed-Rank Test was used for univariate analysis to look for association of absolute-neutrophil counts, total white counts and creatinine values. Correlation values pre and post induction chemotherapy were analyzed. A value of $p < 0.05$ was considered significant.

Results

Patient demographics

Fourteen patients ($n=14$) were included in this study. Overall, the median age of patient was 41 years (mean: 41.21 ± 12.08) where 57.1% (8) of the patients were female and 42.9% (6) were male (Figures 1 and 2).

At the end of the study, 11 patients were alive (Table 1).

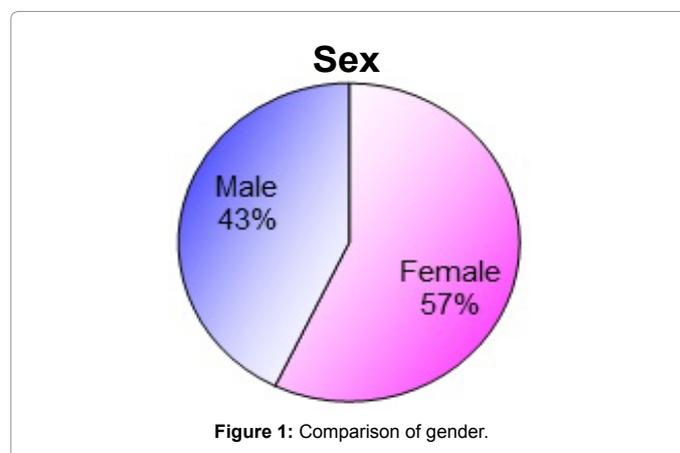


Figure 1: Comparison of gender.

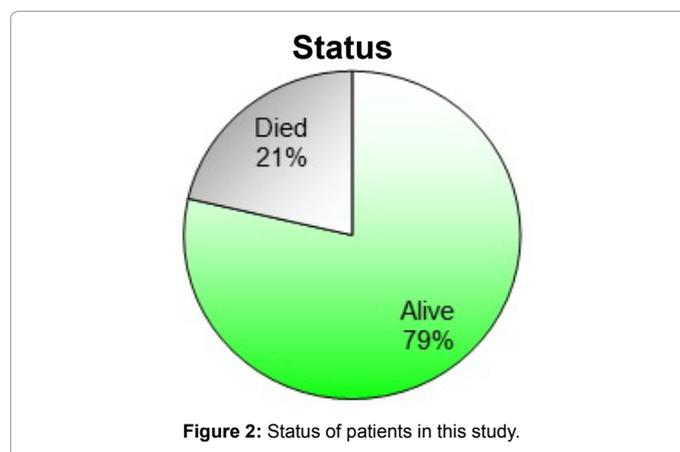


Figure 2: Status of patients in this study.

Patient's comorbids

Eleven patients (78.6%) had no known medication illness prior to being diagnosed with Acute Myeloid Leukemia and induction therapy initiation (Table 2).

One patient has Type 2 Diabetes Mellitus and Gout. One patient had a hemithyroidectomy done. One patient has Benign Prostatic Hyperplasia, Epilepsy and Multinodular Goitre.

Prevalence of sensory-Neural hearing loss

Tuning fork tests: Rinne's test was positive pre and post induction chemotherapy in twelve patients (Table 3). Weber's test was centralised pre and post induction chemotherapy in twelve patients (Table 4). The tuning fork tests were not performed in two patients post induction chemotherapy as both succumbed to complications of acute myeloid leukemia. However, both results could not be interpreted as the constant is the same for both parameters; ie no change pre and post induction chemotherapy.

Pure tone audiometry: A Pure Tone Audiometry was done pre and post induction treatment (Table 5). Prior to induction treatment, ten patients had normal hearing and four patients had pre-existing sensori-neural hearing loss. Post induction treatment, there was no worsening of pre-treatment hearing loss. One patient had improvement of hearing after treatment initiation but passed away post-induction chemotherapy. Two patients succumbed to complications of induction chemotherapy and did not participate in the post treatment audiometry test. This was statistically significant ($p=0.001$) when analysed with Chi-Square Tests and paired with Pearson Chi-Square (value 34.440), Likelihood Ratio (value 18.568) and Linear-By-Linear Association (value 5.466) Table 6 which shows there is no evidence of sensori-neural hearing loss pre and post induction chemotherapy.

Comparison of patient's parameters pre and post induction chemotherapy

Absolute neutrophil count (ANC): Overall, there was a reduction in patients' ANC (Table 7). However, Wilcoxon Signed-Rank Test showed statistically significant changes of patients' ANC pre and post induction chemotherapy ($Z=-2.485$, $p=0.013$) (Table 8).

Total white counts: Overall, there was a reduction in patients' Total White Counts (Table 9). However, Wilcoxon Signed-Rank Test showed statistically significant changes of patients' Total White Count pre and post induction chemotherapy ($Z=-3.233$, $p=0.001$) (Table 10).

Haemoglobin counts: Overall, there was a reduction in patients' Haemoglobin Counts (Table 11). However, Wilcoxon Signed-Rank Test showed statistically significant changes of patients' Haemoglobin Count pre and post induction chemotherapy ($Z=-2.097$, $p=0.036$) (Table 12).

Platelet counts: Overall, there was an increase in patients' Platelet Counts (Table 13). However, Wilcoxon Signed-Rank Test showed statistically not-significant changes of patients' Platelet Counts pre and post induction chemotherapy ($Z=-1.130$, $p=0.258$) (Table 14).

Creatinine levels: Overall, there was a reduction in patients' Creatinine levels (Table 15). However, Wilcoxon Signed-Rank Test showed statistically significant changes of patients' ANC pre-and post-induction chemotherapy ($Z=-2.386$, $p=0.017$) (Table 16).

Morbidity and mortality

There were 3 mortalities. One patient completed induction treatment and two patients only managed to complete the pre-induction treatment. The cause of death was due to neutropenic sepsis.

Variables	No.	Percent (%)
Sex		
Female	8	57.1
Male	6	42.9
Status		
Alive	11	78.6
Died	3	21.4
Age		
Mean \pm SD	41.21 \pm 12.08	

Table 1: Gender, study participants status and age distribution.

Comorbidities	No.	Percent (%)
NKMI	11	78.6
BPH/Epilepsy/Nodular goiter	1	7.1
Partial thyroidectomy 99'	1	7.1
DM, gout	1	7.1

Table 2: Comorbidity of patients enrolled.

Pre-Chemo Rinne's Test* Post-Chemo Rinne's Test Cross Tabulation			
Count	Post-Chemo Rinne's Test		Total
	Positive	NA	
Pre-Chemo Rinne's test	12	2	14
Total	12	2	14

Table 3: Rinne's test pre and post induction chemotherapy.

Pre-Chemo Weber's Test* Post-Chemo Weber's Test Cross Tabulation			
Count	Post-Chemo Weber's Test		Total
	Positive	NA	
Pre-Chemo Weber's Test Positive	12	2	14
Total	12	2	14

Table 4: Weber's test pre and post induction chemotherapy.

Pre D & A	Post D & A
Normal	Normal
Bilateral mild-mixed sensory neural hearing loss	Normal
Normal	Normal
Normal	NA
Normal	normal
Normal	Normal
Mild to profound sloping sensory neural hearing loss	NA
Normal	Normal
Mild to moderate sensory neural hearing loss	Mild to moderate sensory neural hearing loss
Bilaterally sloping sensory neural hearing loss	Bilaterally sloping sensory neural hearing loss
Normal	normal

Table 5: Audiogram results pre and post induction chemotherapy.

I) Pre D & A * Post D & A Cross Tabulation				
Variables		Post D & A		Total
		Normal	Mild to moderate sensory neural hearing loss	
Pre D & A	Normal	9	0	10
	Bilateral mild-mixed sensory neural hearing loss	1	0	1
	Mild to profound sloping sensory neural hearing loss	0	0	1
	Mild to moderate sensory neural hearing loss	0	1	1
	Bilaterally sloping sensory neural hearing loss	0	0	1
Total		10	1	14

II) Chi-Square Tests			
Variables	Value	df	Asymp. Sig. (2 sided) ^a
Pearson Chi square	34.44	12	0.001
Likelihood ratio	18.568	12	0.1
Linear-linear by association	5.466	1	0.019
N of valid cases	14		

Note: ^a 19 cells (95.0%) have expected count less than 5. The minimum expected count is 0.07

Table 6: a) Comparison of pre and post induction chemotherapy showing no evidence of sensory-neural hearing loss which is b) statistically significant (p=0.001).

Pre-Chemo	Post-Chemo
Absolute Neutrophil Count	Absolute Neutrophil Count
6.3	0.2
0.8	0.1
4.6	0.1
0.1	0
1.1	2.5
5.7	0.2
0.3	0
0.4	0.3
6	0.5
0.8	0
0	0
6.5	0.2
2.5	2.6
0.8	0

Table 7: Absolute neutrophil counts pre and post induction chemotherapy.

I) Ranks				
Variables	Ranks	N	Mean Ranks	Sum of Ranks
Absolute Neutrophil	Negative Ranks	11 ^a	7.36	81
Count Post Chemo	Positive Ranks	2 ^b	5	10
Absolute Neutrophil	Ties	1 ^c	--	--
Count Pre Chemo	Total	14	--	--

^aAbsolute Neutrophil Count - Post Chemo < Absolute Neutrophil Count - Pre Chemo
^bAbsolute Neutrophil Count - Post Chemo > Absolute Neutrophil Count - Pre Chemo
^cAbsolute Neutrophil Count - Post Chemo = Absolute Neutrophil Count - Pre Chemo

II) Test Statistics ^b	
Variables	Absolute Neutrophil Count- Post- Chemo- Absolute Neutrophil count- Pre- Chemo
Z	-2.485 ^a
Asymp. Sig. (2-tailed)	0.013

^a Based on positive ranks
^b Wilcoxon Signed Ranks Test

Table 8: Comparison of pre and post induction chemotherapy showing derangement in ANC which is statistically significant (p=0.013).

Pre-Chemo	Post-Chemo
Total White	Total White
37.2	1.4
19.5	1.5
21.6	1.3
1.5	0.1
73.4	5.4
21.1	0.6
4.2	0.6
24.6	1
8	0.6
4.6	0.4
4.4	0.5
33.2	0.6
3.8	4.4
7	0.5

Table 9: Total white counts pre and post induction chemotherapy.

I) Ranks				
Variables		N	Mean Rank	Sum of Ranks
Total White- Post-Chemo- Total White -Pre-Chemo	Negative Ranks	13 ^a	8.00	104.00
	Positive ranks	1 ^b	1.00	1.00
	Ties	0 ^c	--	--
	Total	14	--	--

^a Total White - Post-Chemo < Total White-Pre-Chemo

^b Total White - Post-Chemo > Total White-Pre-Chemo

^c Total White - Post-Chemo = Total White-Pre-Chemo

II) Test Statistics ^b	
Variables	Total White-Post-Chemo- Total White -Pre-Chemo
Z	-3.233 ^a
A symp. Sig. (2-tailed)	0.001

^a Based on Positive Ranks

^b Wilcoxon Signed Ranks Test

Table 10: Comparison of pre and post induction chemotherapy showing derangement in Total White Count which is statistically significant ($p=0.001$) 2.097, $p=0.036$).

Pre-Chemo Haemoglobin (g/dL)	Post-Chemo Haemoglobin (g/dL)
7.6	7.9
11.1	6.9
8.9	7.5
9.2	8.6
12.1	9.4
7.9	7.9
7.5	8.6
9.4	8.2
10.7	7.2
8.3	7.6
9.6	8.1
7.6	7.3
6.1	7.8
9.1	7.2

Table 11: Haemoglobin counts pre and post induction chemotherapy.

I) Ranks			
Variables	N	Mean Rank	Sum of Ranks
Haemoglobin- Post-Chemo- Haemoglobin -Pre-Chemo	Negative Ranks	10 ^a	75.50
	Positive ranks	3 ^b	15.50
	Ties	1 ^c	--
	Total	14	--

^a Haemoglobin - Post-Chemo <Haemoglobin -Pre-Chemo
^b Haemoglobin - Post-Chemo >Haemoglobin -Pre-Chemo
^c Haemoglobin - Post-Chemo = Haemoglobin -Pre-Chemo

I) Test Statistics ^b	
Variables	Haemoglobin-Post-Chemo-Haemoglobin-Pre-Chemo
Z	-2.097 ^a
A symp. Sig. (2-tailed)	0.036

^a Based on Positive Ranks
^b Wilcoxon Signed Ranks Test

Table 12: Comparison of pre and post induction chemotherapy showing derangement in Haemoglobin count which is statistically significant (p=0.036).

Pre-Chemo Platelets	Post-Chemo Platelets
38	83
23	30
36	8
95	14
46	120
157	4
24	88
22	15
105	21
61	12
64	12
10	26
8	37
209	6

Table 13: Platelet counts pre and post induction chemotherapy.

I) Ranks			
Variables	N	Mean Rank	Sum of Ranks
Platelets- Post-Chemo- Platelets-Pre-Chemo	Negative Ranks	8 ^a	70.50
	Positive ranks	6 ^b	34.50
	Ties	0 ^c	
	Total	14	

^a Platelets- Post-Chemo < Platelets-Pre-Chemo
^b Platelets- Post-Chemo > Platelets-Pre-Chemo
^c Platelets- Post-Chemo = Platelets-Pre-Chemo

I) Test Statistics ^b	
Variables	Platelets- Post-Chemo-Platelets-Pre-Chemo
Z	-1.130 ^a
A symp. Sig. (2-tailed)	0.258

^a Based on Positive Ranks
^b Wilcoxon Signed Ranks Test

Table 14: Comparison of pre and post induction chemotherapy showing derangement in platelet count which is statistically not-significant (p=0.017).

Pre Urea/Creatinine (mmol/L / ml/min)	Post Urea/Creatinine (Pre Urea mmol/L / Creatinine ml/min)
2.1/52	3.2/51
1.7/51	2.6/43
5.3/68	5.2/65
3.6/80	4.6/67
2.6/78	2.4/36
1.0/39	1.6/40
3.7/84	2.3/82
5.0/81	4.8/54
5.2/55	4.6/46
2.8/51	2.3/44
2.7/65	3.8/98
4.7/93	3.1/83
2.9/75	4.5/64
1.8/60	1.8/31

Table 15: Creatinine levels pre and post induction chemotherapy.

I) Ranks			
Variables	N	Mean Rank	Sum of Ranks
Post Creat-Pre Creat Negative Ranks	Negative ranks	12 ^a	7.54
	Positive ranks	2 ^b	7.25
	Ties	0 ^c	
	Total	14	

^a Post Creat < Pre Creat
^b Post Creat > Pre Creat
^c Post Creat = Pre Creat

II) Test Statistics ^b	
Variables	Post Creat - Pre Creat
Z	-2.386 ^a
A symp. Sig. (2-tailed)	0.017

^a Based on Positive Ranks
^b Wilcoxon Signed Ranks Test

Table 16: Comparison of pre and post induction chemotherapy showing derangement in creatinine count which is statistically significant (p=0.017).

Discussion

Acute Myeloid Leukemia is the most common haematological malignancy encountered by the Haematology Department in Ampang Hospital. Treatment protocols comprises of anthracycline and anthracenedione administration. Prior to this, there are no attributes of side effects of Acute Myeloid Leukemia chemotherapy agents causing sensorineural hearing loss [1,2]. Treatment of AML with Daunorubicin and Cytarabine (ARA-C) as induction protocols offer the initial remission and overall survival. Kaspers et al. analyzed data from 13 original manuscripts of centers in AML therapy. Therapy constitutes of intensive courses of chemotherapy based on cytarabine and an anthracycline achieved mainly complete remission with reduced side effects and high-quality cure [8]. If these patients develop partial remission or relapse, further consolidation protocols are administered.

The purpose of this research is to study the prevalence of sensori-neural hearing loss pre and post induction treatment chemotherapy. Secondary outcomes of demographic and other parameters were included to compound this study. In our study, pure tone audiometry is done prior to treatment induction and post induction treatment

(Day 10). For ototoxic insults resulting from anticancer chemotherapy, significant hearing threshold shifts occur at the highest measurable frequencies and then spread to lower frequencies with further drug exposure. High-frequency (8 kHz) pure-tone audiometry (HFPTA) has been successfully applied to adults for the purpose of identifying significant threshold shifts caused by ototoxicity [10]. Thus, HFPTA holds promise as a useful tool to detect hearing damage at the earliest possible time.

From our study population, 14 subjects were enrolled. Unfortunately, 2 succumbed to disease process and were not able to complete the study. From our observation, there is no evidence of ototoxicity from induction therapy of Daunorubicin and Cytarabine (ARA-C) in our study population. In fact, 1 patient developed hearing improvement post induction treatment. It is exactly unknown to us as to how this patient had an improvement in his hearing. We wished to follow-up this subject during surveillance. However, the patient succumbed to disease complications. Therefore, we concluded that Daunorubicin and Cytarabine (ARA-C) does not cause sensori-neural hearing loss in Acute Myeloid Leukemia patients during the induction treatment. The prevalence of sensori-neural hearing loss in this study population is 71.4%.

Regarding secondary outcomes, the mean age is of 41 years old with predominant females. Overall levels of Absolute Neutrophils Counts, Total White Counts, Haemoglobin Counts and Creatinine Levels are less when compared to pre and post induction treatment. This can be attributed to the disease process per-se. The Platelet Counts are increased but not statistically significant. Therefore, it can be concluded that Daunorubicin and Cytarabine (ARA-C) shows statistically significant reduction in Absolute Neutrophils Counts, Total White Counts, Haemoglobin Counts and Creatinine levels in our study population.

There was no need for intervention from AML induced toxicity, as evidence by the study population.

Limitations to this study is a small sample size. Despite being the commonest malignancy encountered by the department, many patients were not fit to undergo curative or palliative chemotherapy. Hence, 14 subjects were recruited. Also, this hearing comparison was only done in the induction phase of treatment initiation. We would prefer if we could follow up these patients either during complete remission or partial remission and it would be ideal if this study is continued in patients receiving stem cell transplant. We would prefer a larger sample size and a longer follow up in the future, up to at least 3 years, so that the power of the study is better.

Tuning fork tests are simple and inexpensive tools to identify the prevalence of sensori-neural hearing loss. However, the usage of High Frequency Pure Tone Audiometry as an assessment of ototoxicity in our patients is a subject of cost. This may not be available in all centers, thus limiting the screening for such patients. We were fortunate enough to have this service and will certainly hope to follow up on our subjects on the long term.

Conclusion

Daunorubicin and Cytarabine (ARA-C) in combination does not cause sensori-neural hearing loss in Acute Myeloid Leukemia patients during the induction treatment. It will be interesting to follow up these subjects and new recruits on a longer duration with disease remission or relapse and after stem cell transplant to postulate the prevalence of ototoxicity.

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Nil.

Conflicts of Interest

There are no conflicts of interest.

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