Comparing Long Term Treatment Outcomes of Patients with Acute Myelogenous Leukemia who received Doxorubicin and Cytarabine Induction Chemotherapy Compared with First-Line Regimen Idarubicin plus Cytarabine: A Retrospective Cohort Study

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Abstract

Rationale and Objectives. The burden of acute myeloid leukemia (AML) is felt worldwide with increasing number of diagnosed cases. A recommended treatment option for a longer remission is hematopoietic stem cell transplantation after chemotherapy with cytarabine and an anthracycline antibiotic, either Idarubicin or Daunorubicin. In the Philippines, Doxorubicin, a cheaper and more accessible option for chemotherapy among those who have financial incapabilities. It is no longer part of the National Comprehensive Cancer Network (NCCN) recommendation for use however; it remains to be part of the Philippine National Clinical Practice Guideline in the treatment of AML. This leads us to wonder what the difference in outcome of patients who have received doxorubicin compared to those who received Idarubicin as induction chemotherapy.

Research Design and Methodology. This is a retrospective cohort study. Data was collected through chart review of AML patients admitted for induction chemotherapy. Descriptive statistics was used to analyze the sociodemographic and clinical profile of patients. Survival analysis was done using the Kaplan-Meier computation. The t-test for two proportions was used to compare outcomes between the two groups.

Results. This study included 65 participants, 55 received idarubicin and 10 received doxorubicin. The average age of diagnosis in the Idarubicin group is 41.38 years, and 34.9 years in the Doxorubicin group. Majority of participants are females (58.18% vs 80%) and married (67.27% vs 60%). They are predominantly nonsmokers (89.09% vs 80%), with no maintenance medications (61.82% vs 70%), and comorbidities (70.91% vs 90%). There was no significant difference in the median overall survival of both groups (507 days vs 428 days, logrank test = 0.74).

Discussion and Conclusion. Outcomes of this study leads us to conclude that Doxorubicin is not inferior to Idarubicin in terms of survival.

Keywords. *Acute myelogenous leukemia, Idarubicin, Doxorubicin, induction chemotherapy, survival,*

Introduction

Acute myeloid leukemia (AML) is the most common leukemia among the adult population. It results from the clonal expansion of immature myeloid cells in the peripheral blood and bone marrow. This accounts for 80% of all adult leukemias worldwide.[10] The burden of leukemia is felt worldwide. Globally, the number of diagnosed leukemia cases has been increasing in number. According to the 2022 AML Statistics, an estimate of 20,050 people of all ages in the United States will be diagnosed this 2022 with AML. Locally, the Philippines has been experiencing an increase in AML cases every year as well. Based on the 2015 Philippine Cancer Facts and Estimates approximately 43,058 male population and 55,191 female population of cancer cases are diagnosed in the year 2012. The highest

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number of cases were found to affect patients ≥75 years old of both genders. Approximately 5% of male Filipinos and 3.8% of female Filipinos are diagnosed with leukemia every year and has contributed to the 5.7% deaths in a year.[6]

Eligible patients with standard risk AML are advised hematopoietic stem cell transplantation after chemotherapy for a longer remission. This is the only regimen with a chance of cure. A specific treatment option from the National Comprehensive Cancer Network (NCCN) guidelines include the use of a combination anthracycline antibiotic with cytarabine as intensive treatment to induce remission.[7] This has provided a 67% complete response when used. There are two anthracycline antibiotics currently available for acute myeloid leukemia, Idarubicin and Daunorubicin. Idarubicin in combination with cytarabine has been a first-line treatment recommendation for patients eligible for intensive induction therapy.[11] This has provided 70% complete remission rate and has been found to be superior than Daunorubicin. Daunorubicin is currently not available in the Philippine market but its use has resulted to a 59% complete remission. A third earlier anthracycline drug, Doxorubicin, has had a declining use due to its concomitant long term side effects. Although, there are studies that show no significant difference in the outcome and toxicity profile of both drugs, it is not currently recommended as a first line treatment for induction chemotherapy among international cancer guidelines.[8] However, clinicians with patients who are financially constrained are still drawn to its use because of its cost and availability. It is actually a part of the Philippine National Clinical Practice Guidelines for AML recommendation to start induction chemotherapy with either idarubicin, daunorubicin, or doxorubicin among patients < 60 years old with favorable or intermediate risk cytogenetics.

A study comparing Idarubicin and Doxorubicin in Egypt showed that approximately 67.1% of patients on doxorubicin achieved complete remission compared to the 68.7% remission rate achieved by the group receiving Idarubicin. Although, idarubicin combination chemotherapy did cause less adverse effects (nausea, vomiting, stomatitis, neutropenia, clinical cardiotoxicity), there was no statistically significant difference in overall response between the two regimens. There is no current study in the Philippines with the same objective.

Methods

We did a retrospective cohort study comparing outcomes of patients with AML who received induction chemotherapy of cytarabine combined with Idarubicin or Doxorubicin. Data was collected from charts of admitted AML patients 18 years old and above who underwent induction chemotherapy within the years 2012 to 2023 at University of Santo Tomas Hospital private and clinical division. Follow-up data was obtained through their outpatient charts obtained from the clinics of their respective physicians. A total of 633 charts were reviewed, but only 65 charts were included in the study. Participants diagnosed with AML who were not included in the study either received a different induction protocol, is ongoing consolidation chemotherapy, did not receive any chemotherapy at all, or was admitted for a different reason such as a concurrent infection. Cytogenetic studies such as karyotyping and fluorescent in situ hybridization for AML were not done in all patients included in the study, hence, patients were not categorized based on their risk category.

Data was collected through chart review and was encoded using a data collection form. Demographic profile such as age, sex, marital status, and educational background were obtained. Clinical data such us number of co-morbidities and number of maintenance medications were recorded. Majority of the patients had no bone marrow biopsy, cytogenetic tests and molecular tests results attached to their charts. Majority of patients had no results attached confirming the type of response they had after chemotherapy, hence outcomes measured was only limited to overall survival and number of days of survival after initiation of day 1 chemotherapy. Additional information after discharge was obtained from their outpatient records. Data regarding the patient's date of death and last date of follow-up were obtained. Identifiers were removed from the collected data. Data collection forms were locked in file cabinets and will be kept for three years from the finalization of this paper.

The study used various statistical tools. Descriptive statistics was used to analyze the sociodemographic and clinical profile of patients. Mean and standard deviation was used for the continuous data, and frequency and percent for categorical data. Survival analysis was done using the Kaplan-Meier computation. The t-test for two proportions was used to compare outcomes between the two groups.

Ethical Considerations

This study was performed in compliance to the following local and international ethical guidelines for research ethics: Declaration of Helsinki 2015, International Conference on Harmonization on Good Clinical Practice (ICH-GCP), Council for International Organizations for Medical Sciences 2016, Good Research Practice (GRP), Philippine National Ethical Guidelines for Health and Health-Related Research of 2017, Philippine Data Privacy Act of 2012 and its Implementing Rules and Regulations (IRR) of 2016. This was reviewed and approved by the IRB of UST Hospital.

Results

Sociodemographic and Clinical Profile. This study included 65 patients who were admitted at USTH private and clinical division who were confirmed to have acute myelogenous leukemia through bone marrow aspiration and biopsy and flow cytometry. Fifty-five of the patients received Idarubicin with cytarabine and ten received Doxorubicin and cytarabine. No patient received bone marrow or hematopoietic stem cell transplantation after induction chemotherapy.

Table I. Sociodemographic Profile

	Idarubicin (55)	Doxorubicin (10)	p-value
Age	41.38 ± 14.25	34.9 ± 9.46	0.09
Sex			0.34
Male	23 (41.82%)	2 (20%)	
Female	32 (58.18%)	8 (80%)	
Marital Status			0.79
Single	16 (29.09%)	4 (40%)	
Married	37 (67.27%)	6 (60%)	
Separated	2 (3.64%)	0	
Widowed	0	0	
Educational background			0.38
Primary	0	0	
Secondary	3 (5.45%)	0	
College	26 (47.27%)	6 (60%)	
Vocational	0	0	
Doctorate	1 (1.82%)	1 (10%)	
Unknown	25 (45.45%)	3 (30%)	
Smoker			0.31
Yes	6 (10.91%)	2 (20%)	
No	49 (89.09%)	8 (80%)	
Number of Comorbidities			0.31
0	34 (61.82%)	7 (70%)	
1-2	16 (29.09%)	2 (20%)	
≥ 3	5 (9.09%)	1 (10%)	
Number of Maintenance Medications			0.37
0	39 (70.91%)	9 (90%)	
1-2	12 (21.82%)	0	
≥ 3	4 (7.27%)	1 (10%)	

Table II. Clinical Profile

	Idarubicin (55)	Doxorubicin (10)	p-value
Number of Transfusions			
PRBC (no. of units)	6.11 ± 5.21	4.4 ± 3.06	0.17
Platelet Concentrate (no. of units)	22.91 ± 24.54	21.5 ± 19.80	0.85
Platelet Apheresis (no. of units)	2.16 ± 2.71	1 ± 1.25	0.04
GCSF (no of days given)	6.38 ± 6.52	8.2 ± 4.61	0.30
Antimicrobial Therapy			
No. of IV antibiotics	2.35 ± 1.66	1.4 ± 0.84	0.01
No. of PO antibiotics	1.24 ± 1.07	1.5 ± 1.08	0.49
No. of Antiviral medications	0.44 ± 0.63	0.5 ± 0.71	0.79
No. of Antifungal medications	0.74 ± 0.75	0.9 ± 0.7	0.55
Anti-tuberculosis treatment			0.34
Yes	8 (14.55%)	0	
No	47 (85.45%)	10 (100%)	
CBC			
Hgb	81.20 ± 14.60	87.2± 22.81	0.44
WBC	37.31± 53.32	55.77 ± 64.00	0.41
Platelet	81.2 ± 90.49	110.9 ± 68.50	0.25
Blast	20.27 ± 23.87	37.3 ±31.41	0.13

Table I shows the sociodemographic profile of both groups. The average age of diagnosis in the Idarubicin group is 41.38, and 34.9 in the Doxorubicin group. Majority of patients were females (58.18% vs 80%, p-value = 0.34) and married (67.27% vs 60%, p-value=0.79). Patients in both groups are predominantly nonsmokers (89.09% vs 80%, p-value=0.31), with no maintenance medications (61.82% vs 70%, p-value=0.31), and no comorbidities (70.91% vs 90%, p-value=0.37).

Clinical profile of both groups during their course of admission is shown in Table 2. Complete blood count is measured prior to induction therapy. The average blood count levels measured showed no significant difference in hemoglobin (81.2 ± 14.6 vs 87.2 ± 22.81, *p=0.44*), white blood cell count (37.31 ± 53.32 vs 55.77 ± 64, *p=0.41*), platelet levels (81.2 ± 90.49 vs 110.9 ± 68.5, *p=0.25*) and blast count (20.27 ± 23.87 vs 37.3 ± 31.41, *p=0.13*). Both groups received blood transfusions during induction chemotherapy. There was no significant difference in the number of pRBC and platelet concentrate transfused between two groups. Patients in

Table III. Outcome of Patients at 90, 180, and 365 Days

	Idarubicin (55)	Doxorubicin (15)	p-value
Outcome in 90 Days (3 months)			0.64
Alive	32 (58.18%)	5 (50%)	
Expired	14 (25.45%)	2 (20%)	
Lost to Follow-up	9 (16.36)	3 (30%)	
Outcome in 180 days (6 months)			0.92
Alive	22 (40%)	4 (40%)	
Expired	14 (25.45%)	2 (20%)	
Lost to Follow-up	19 (34.55%)	4 (40%)	
Outcome in 365 days (1 year)			0.74
Alive	16 (29.09%)	2 (20%)	
Expired	18 (32.73%)	2 (20%)	
Lost to Follow-up	21 (38.18%)	6 (60%)	

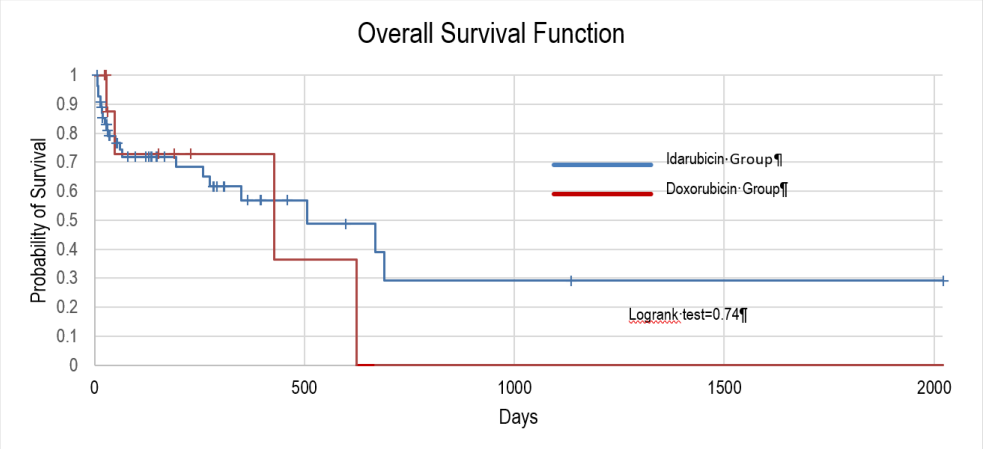


Figure 1. Overall Survival Function of Idarubicin and Doxorubicin Group

the Idarubicin group received more platelet apheresis (2.16 ± 2.71 vs 1.0 ± 1.25, *p=0.04*) compared to the Doxorubicin group. There was no significant difference in the number of days GCSF was given in both groups (6.38 ± 6.52 vs 8.2 ± 4.61, *p=0.85*). The Idarubicin group were prescribed with more intravenous antibiotics (2.35 ± 1.66 vs 1.4 ± 0.84, *p=0.01*). Majority of the participants were not started on anti-tuberculosis treatment.

Survival. The primary outcome of this study includes comparison of overall survival among both groups. Out of the 65 patients, two patients from the Idarubicin group had the longest days of survival at 2020 days. Upon the completion of data collection, 4 (40%) of the patients in the Doxorubicin group have expired and 6 (60%) are lost to follow-up. The longest recorded survival in the Doxorubicin group is at 624 days. In the Idarubicin group, after the completion of data collection, 10(18%) were still alive, 21 (38%) has expired and 24 (44%) were lost to follow-up.

Table III shows patient outcomes of both groups in 90 days, 180 days, and 365 days from Day 1 induction chemotherapy. Approximately 50% of both groups are alive after 90 days of chemotherapy. There is no significant difference in the number of deaths in both groups whether at 90 days, 180 days, or 365 days from induction chemotherapy. In the first 90 days, approximately 20% of patients have expired in both groups. with no marked increase in number of deaths. At 365 days, majority of patients are lost to follow-up (38.18% vs 60%, *p=0.74*).

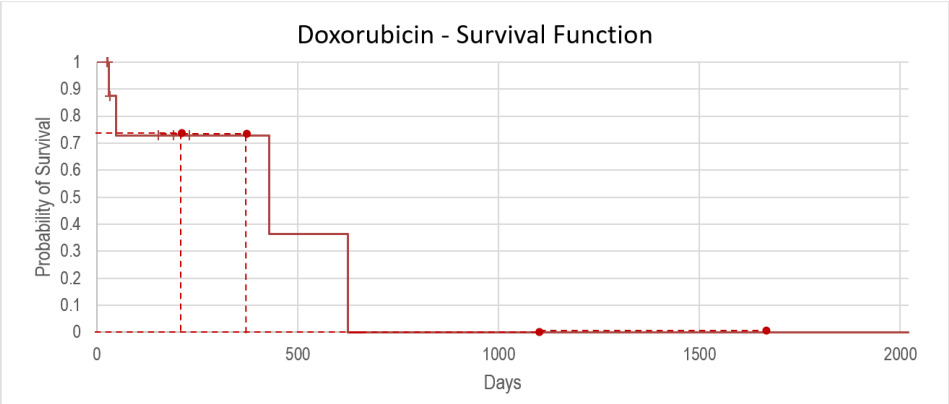
Figure 1 shows the probability of survival of groups who received Idarubicin versus those who received Doxorubicin in combination with cytarabine for induction chemotherapy. There was no significant difference in the median overall survival of both groups (507 days vs 428 days, logrank test = 0.74).

Figure 2 shows the survival of the Doxorubicin group. The probability of survival within the first year from induction chemotherapy is at 73%. The probability of survival decreased to 0% afterwards.

Figure 3 shows the probability of survival of the Idarubicin group. Probability of survival is highest within the first 6 months at 68% gradually decreasing to a lowest probability of 29% at 3-years and 5-years after induction chemotherapy.

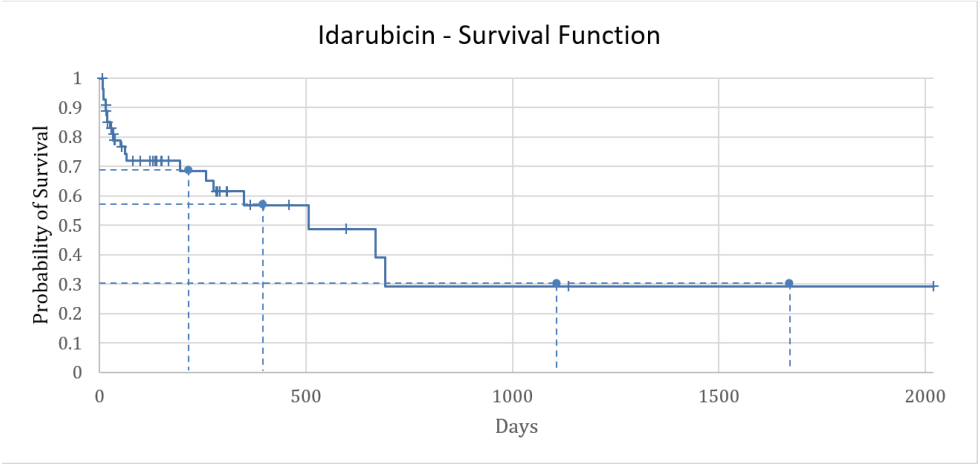
Discussion

Acute Myeloid Leukemia, being the most common leukemia among the adults has been a constant burden



Probability of Survival at 190 days (6 months)	73%
Probability of Survival at 365 days (1 year)	73%
Probability of Survival at 1,095 days (3 years)	0
Probability of Survival at 1,825 days (5 years)	0

Figure 2. Survival Function of Doxorubicin Group



Probability of Survival at 190 days (6 months)	68%
Probability of Survival at 365 days (1 year)	56%
Probability of Survival at 1,095 days (3 years)	29%
Probability of Survival at 1,825 days (5 years)	29%

Figure 2. Survival Function of Doxorubicin Group

for affected individuals. A chance of cure can be achieved through the NCCN recommendation of chemotherapy followed by hematopoietic stem cell transplantation for eligible AML patients.[7] An induction chemotherapy with the combination cytarabine for 7 days and an anthracycline antibiotic (Idarubicin or Daunorubicin) for 3 days is recommended as first-line treatment. This is the current standard of care practiced by Hematologists in the Philippines.[3] Doxorubicin has had decreasing use in developed countries because of its long-term toxicity. Being a third world country where poverty is prevalent, an option of a cheaper chemotherapeutic medication is preferred. There are limited studies comparing Idarubicin and Doxorubicin.

Data from this study shows that patients on Doxorubicin had a higher probability of survival at 73% within in the first-year post-induction chemotherapy. However, this trend abruptly decreased to 0 probability of survival at 3-years and 5-years from induction chemotherapy. The Idarubicin group also had a decreasing probability of survival from 68% on the first 6 months of treatment to 29% probability at 3 years and 5 years from induction chemotherapy. There is however no significant difference in the median overall survival of patients who received either Idarubicin or Doxorubicin (507 days vs 428 days, logrank test = 0.74) in combination with Cytarabine during their induction chemotherapy. This data is congruent with the study of Sherif which showed that although idarubicin combination chemotherapy did cause less adverse effects (nausea, vomiting, stomatitis, neutropenia, clinical cardiotoxicity), there is no statistically significant difference between the two regimens.[8]

Conclusion

Outcomes of this study leads us to conclude that Doxorubicin is not inferior to Idarubicin in terms of overall survival when used as part of the induction chemotherapy among AML patients. The probability of survival, however, is lower in the Doxorubicin group after 3 years and 5 years from day 1 induction chemotherapy when compared with the Idarubicin group. This strengthens the current international recommendation of giving Idarubicin as frontline induction chemotherapy for AML patients. Investigators of this study encourages the use of Idarubicin among patients who have the resource to obtain the drug and reserve Doxorubicin to those who are incapable of providing so.

Recommendations

Being a retrospective study, data was obtained only from the information available from the charts. A prospective study which can actively follow patients' course during induction chemotherapy, the side effects, drug-induced toxicity, treatment response and survival is recommended. A multi-center study involving private and government hospitals may provide more significant findings.

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