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*Research Article*

# Idarubicin versus Doxorubicin in Acute Myeloid Leukemia: A Parallel Randomized Trial with Pharmacoeconomic Analysis

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**Abstract**

***Background:*** Acute Myeloid Leukemia (AML) is the most common form of acute leukemia among adults. Treatment of acute leukemia has been divided into induction chemotherapy and post-remission therapy. The goal of induction chemotherapy, that consists of anthracycline and cytarabine, is to achieve morphologic complete remission (CR), but the main problem is that it has a high economic burden. Idarubicin is the anthracycline of choice used in AML, while doxorubicin, is mainly used in other types of cancer. The aims of this study were evaluating the use of doxorubicin versus idarubicin in the induction phase for the treatment of AML and analysis the impact of the adoption of this anthracycline in Egypt's public health system.

***Methods:*** A randomized controlled trial was undertaken in 244 patients with AML. A decision tree was developed based on the clinical outcome of the study, safety and efficacy, aiming to get the expected cost of doxorubicin compared with idarubicin in AML management.

***Results:*** In the doxorubicin group, 52.5% had a CR, versus 49.2 % in the idarubicin group (P=0.6). The most common toxicities among the 2 groups were febrile neutropenia, diarrhea and vomiting. Oral mucositis (OM) was higher in the doxorubicin group (70.8% vs 37%, P=0.0001), while invasive fungal infections were greater in the idarubicin group (75% vs 88.7%, P=0.004). Doxorubicin arm had a lower cost than idarubicin arm in treatment success group (39,492 LE vs 44,323 LE).

***Conclusion:*** Doxorubicin provides a treatment option with comparable efficacy, toxicity profile and survival rates at a lower cost compared to the traditional treatment, idarubicin.

## Introduction

Acute Myeloid Leukemia (AML) is the most common form of acute leukemia among adults.[1] AML refers to a collection of neoplasms arising from a clonal, myeloid-committed, hematopoietic precursor whose behavior is characterized by a dramatic proliferative advantage and maturation arrest.[2]

Treatment of acute leukemia has been divided into induction chemotherapy and post-remission (i.e., consolidation) therapy. The goal of induction chemotherapy is to achieve morphologic complete remission (CR).[3,4] The induction phase is a challenging phase because of the high rate of complications, due to the active disease and the active treatment. Thus, a major problem in acute leukemia treatment is the economic burden of the induction phase. During this phase, the patient requires hospitalization for about one month receiving chemotherapy, blood products, supportive treatments, hydration, antibiotics, antifungals and, in sometimes, antivirals, beside the daily laboratory work and per required radiological studies and investigations.[5]

Despite targeted strategies employed in recent studies in the light of cytogenetics and molecular abnormalities, the most widely used induction therapy remains the so-called '7 + 3' regimen.[3] This has traditionally included a 7-day continuous infusion of cytarabine plus an anthracycline on days 1 to 3.[6] For almost 40 years, this combination has remained the mainstay of induction therapy in AML and yielded initial response rates from 50% to 75%.[7]

The National Comprehensive Cancer Network (NCCN) recommends the use of idarubicin (Ida) 12 mg/m$^2$ as the first-line induction anthracycline agent in 7+3 protocol for AML.[8] Daunorubicin was previously used until idarubicin was proven more effective while doxorubicin (Dox) had controversial results.[9] Both Dox and Ida are anthracyclines that work on cancer cells by intercalating into DNA to disrupt the topoisomerase-II-mediated DNA repair. Ida has the superiority of binding capacity to DNA. Both anthracyclines generate free radicals that cause cellular damage.[7]

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For economic and local reasons, Dox is still used in Egypt as the anthracycline of choice in AML management. According to a local retrospective study, there is no difference in response rate compared to Ida.[10]

According to the FDA-approved labeling information, Dox has more prevalence of myelosuppression (52%), congestive heart failure (CHF) (9-30%), stomatitis (37%) and fatigue (33%) than Ida. The FDA approved Ida has more prevalence of infection (95%), nausea and vomiting (30-60%), hemorrhage (63%) and alopecia (25-30%). The FDA stated that the prevalence of Dox related nausea and vomiting is 22-37% and for alopecia 15%, and the prevalence of Ida related CHF is only 2%.

To the best of our knowledge, there are only two prospective trials that had compared Ida versus Dox in the treatment of AML. One of them was conducted in South Africa by Bezwoda and Dansey[11], and the other one by Intragumtornchai *et al.*[12] Both trials were conducted on a limited number of patients.

In the light of previous data, this study was conducted to assess the clinical response and toxicity of Ida versus Dox, and to analyze the expected cost of each treatment in the induction phase of treatment of AML patients.

## Methods

This was a prospective parallel randomized study that included all eligible adult acute myeloid leukemia patients admitted to the National Cancer Institute (NCI), Cairo University, during the period from September 2017 to December 2019. The study was conducted according to the Declaration of Helsinki and the guidelines for Good Clinical Practice (2011). The local ethics committee at Faculty of Pharmacy, Cairo University approved the protocol (CL2061), and written informed consent was obtained from all patients prior to enrollment in the study. The trial was registered in the Pan African Trial Registry (PACTR202309818279236).

### *Patients*

Patients were included if they were 18 years or older with confirmed AML diagnosis by bone marrow aspirate (BMA) and immunophenotyping (IPT), and have performance status ≤ 2, according to Eastern Cooperative Oncology Group (ECOG) performance status scale.[13]

Patients with current active second malignancy or AML M3 (Promyelocytic leukemia), or patients with heart failure (low ejection fraction ≤50) were excluded.

The medical staff decided the treatment protocol for the confirmed AML patients to receive either 3 and 7, low dose cytarabine or best supportive care. The eligible 3 and 7 patients then consented for trial participation and simple randomization using flipping a coin was then used to determine the assignment of each participant to either Dox or Ida group as part of their induction therapy. The induction chemotherapy regimen was one cycle of cytarabine 100 mg/m$^2$ as continuous infusion over 24 hours for 7 days + an anthracycline (either Dox 45 mg/m$^2$ or Ida 12 mg/m$^2$) bolus infusion once daily for three days. Doxorubicin dose was calculated in accordance with the local NCI AML protocol.

The patients were followed-up until either: Complete remission after one cycle (about 30 days), Partial remission after one cycle and in this case the patient received another cycle and followed-up (about 60 days), Refractory disease that needs a second line of treatment, HAM (high dose Ara-c 2000 mg/m$^2$ every 12 hrs for 6 doses + Mitoxantrone 12 mg/m$^2$ once daily for 3 days) (about 60 days), or death.

### *Efficacy and safety evaluation*

Baseline assessment included complete history and physical examination and cardiac evaluation by echocardiogram, and laboratory tests: complete blood count (CBC), serum creatinine (Cr), urea, total bilirubin (T.bil), liver enzymes (AST, ALT), electrolytes ($K^+$, $Na^+$, $Ca^{++}$, $PO_4^{-3}$) and uric acid.

Efficacy evaluation was based on response to treatment. BMA was evaluated on day 14 and when CBC is recovered, according to the complete remission (CR) criteria, starting from day 21. If BMA showed no CR on day 14, then the patient received another cycle of chemotherapy, and BMA is reevaluated accordingly, until CR. CR was defined as blast cells in bone marrow ≤ 5%, absolute neutrophil count ≥ 1000/μL and platelets ≥ 100,000/μL. Partial remission (PR) was defined as decrease of at least 50% in the percentage of initial blasts, absolute neutrophil count ≥ 1000/μL and platelets ≥ 100,000/μL. The outcome was considered as refractory disease if no CR or PR.[14] Toxicity was evaluated according to the NCI Common Terminology Criteria for Adverse Events v 5.0.[15] All grades were considered, and any side effect or reaction was evaluated with focus on the following toxicities: Nausea (the urge to vomit) and vomiting (the reflexive act of ejecting the contents of the stomach through the mouth), febrile neutropenia (A disorder characterized by an ANC <1000/mm$^3$ and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.), need for transfusions (packed RBCs transfusion: in case of grade ≥ 3 anemia, platelets transfusion: is indicated to prevent hemorrhage in patients with thrombocytopenia (low platelet count)), oral mucositis (the ulceration or inflammation of the oral mucosa), renal impairment (any kidney injury or elevation in serum creatinine (eGFR) estimated glomerular filtration rate) or creatinine clearance (CrCl) <LLN - 60 ml/min/1.73m$^2$), hepatic dysfunction (any liver injury or elevation in total bilirubin or liver enzymes) and cardiac toxicities (heart failure: the inability of the heart to pump blood at an adequate volume to meet tissue metabolic requirements, left ventricular systolic dysfunction: failure of the left ventricle to produce adequate output. Echocardiogram (Echo) was used for left ventricle ejection fraction (LVEF) assessment. According to the American Heart Association: A LVEF of about 50% to 70% is categorized as normal. A mildly reduced LVEF is usually between 41% and 49%. A

reduced LVEF is usually 40% or less).

### *Survival analysis*

Mortality rate at the end of the follow-up period and time required to enter CR (time to remission), were assessed by BMA starting from day 14 post chemotherapy.

### *Pharmacoeconomic analysis*

From NCI perspective, a decision tree was developed, based on the results of the study, comparing the cost of Dox to the cost of Ida and response for both regimens. All costs were in Egyptian pound (LE) according to the values of 2019. Aiming to demonstrate the perspective of the public health system, the cost values for drugs were obtained from NCI tender costs. The response was either CR, early death or no CR, in which patients received a second line of chemotherapy treatment protocol (HAM: high dose of cytarabine and mitoxantrone). All costs were converted to United States Dollars as well, using the official exchange rate at the time of the study.

The cost of one vial of Dox 50 mg was 72 LE (4.5 $), while the cost of one vial of Ida 10 mg was 633.6 LE (39.6 $). The expected average financial burden of 7+3 regimen using Dox was 530 LE (33.125 $), while the expected average financial burden of 7+3 regimen using Ida was 4030 LE (251.875 $). The financial burden of each outcome (CR, death or no CR) included the sum of cost of hospital and ICU stay, blood components transfused, chemotherapy, supportive drugs, solutions, nutrition solutions, antibiotics, antifungals, laboratory tests, microbiological cultures, radiological studies (CT, MRI, U/S), bone marrow biopsy and aspirate, medical supervision and intensive care unit (ICU) supervision.

The financial burden of adverse events of chemotherapy was calculated depending on the supportive treatments used and the laboratory tests and/or radiological studies used for monitoring the side effect occurred to the patient.

### *Statistical methods*

For sample size calculation, it was assumed that the rate of CR would be increased by 17% in the IDA group, as an estimated average from the two previous studies.[11,12] It was intended to recruit a total of 230 patients, using alpha = 0.05 and power = 0.8. Mean and standard deviation were used for quantitative data, t-test was used for comparison. Chi-square and Fischer exact tests were used for tests of proportion independence. Kaplan-Meier method was used to estimate time to remission. Log rank test was used for comparison of survival curves. P-value was considered significant at 0.05 level.

## Results

### *Patient characteristics*

Two hundred and forty-four AML patients were included in the study and randomized to receive either Dox or Ida as part of their induction chemotherapy treatment. The two arms were balanced at study entry as shown in Table 1, regarding gender, age, weight, height and body surface area (BSA) and prognostic factors (mutated FLT3, inversion (16), translocation (8,21) and FAB classification). Patients presenting with high total leucocytic count (TLC) and/or tumor lysis syndrome (TLS) were also balanced between the 2 groups before starting the chemotherapy. High

**Table 1.** Patient baseline characteristics, prognostic factors and disease related dysfunctions.

| Item | Dox | Ida | P value |
|---|---|---|---|
| Total number | 120 (100%) | 124 (100%) | |
| Male | 68 (56.6%) | 64 (51.6%) | 0.60 |
| Age: Mean (SD) years | 37.48 (11.5) | 40.2 (11.7) | 0.07 |
| Weight: Mean (SD) kg | 72 (16) | 72 (15) | 1.00 |
| Height: Mean (SD) cm | 165 (8) | 164 (9) | 0.36 |
| BSA: Mean (SD) | 1.78 (0.19) | 1.8 (0.2) | 0.40 |
| Mutated FLT 3 | 14 | 9 | 0.28 |
| Inv (16) (+ve) | 5 | 3 | 0.46 |
| Trans (8,21) (+ve) | 10 | 7 | 0.40 |
| FAB Classification: | | | |
| M0 | 4 | 1 | NA |
| M1 | 40 | 37 | |
| M2 | 34 | 39 | |
| M4 | 33 | 31 | |
| M5 | 5 | 9 | |
| M6 | 1 | 1 | |
| M7 | 3 | 6 | |
| Initial TLC count > 100 | 18 (15%) | 14 (11%) | 0.39 |
| TLS | 19 (16%) | 24 (19.4%) | 0.40 |
| Mean baseline LVEF (SD) | 63.16 (4.73) | 63.45 (4.9) | 0.60 |
| Renal impairment (GFR less than 60 ml/min) | 19 (16%) | 24 (19.4%) | 0.40 |
| Hepatic dysfunction | 18 (15%) | 22 (17%) | 0.50 |

Dox: Doxorubicin, Ida: Idarubicin, Pt: Patients, SD: Standard Deviation, kg: Kilograms, cm: centimeters, Inv (16): Inversion (16), +ve: Positive, Trans (8,21): Translocation (8,21), FAB Classification: The French-American-British classification of AML, BSA: Body surface area, TLC: Total leucocytic count, TLS: Tumor lysis syndrome, LVEF: Left ventricular ejection fraction, GFR: glomerular filtration rate.

**Table 2.** Response to Dox and Ida regimens in terms of remission and mortality rates. Presented as number of patients (percentage).

| Item | Dox | Ida | P value[a] |
|---|---|---|---|
| Total number | 120 (100%) | 124 (100%) | |
| CR | 63 (52.5%) | 61 (49.2%) | 0.60 |
| PR | 9 (7.5%) | 8 (6.4%) | 0.70 |
| RD | 6 (5%) | 14 (11.2%) | 0.07 |
| Responsive (CR+PR) | 72 (60%) | 69 (55.6%) | 0.40 |
| No CR (PR+RD) | 15 (12.5%) | 22 (18%) | 0.30 |
| No blasts in D14 | 72 (60%) | 65 (52.4%) | 0.20 |
| Mortality | 42 (35%) | 41 (33%) | 0.70 |

[a]Using Chi square test. Dox: Doxorubicin, Ida: Idarubicin, CR: Complete remission, PR: Partial remission, RD: Refractory disease, D14: Day 14 of starting treatment.

**Table 3.** Treatment Related Toxicities as defined by the NCI Common Terminology Criteria for Adverse Events v 5.0.[15] Presented as number of patients (percentage).

| Item | Dox | Ida | P value[a] |
|---|---|---|---|
| Total number | 120 (100%) | 124 (100%) | |
| Vomiting | 59 (49%) | 63 (50.8%) | 0.40 |
| G I | 8 (6%) | 7 (5.5%) | 0.70 |
| G II | 47 (39%) | 49 (39.5%) | 0.90 |
| G III | 3 (2.5%) | 7 (5.5%) | 0.20 |
| G IV | 1 (0.8%) | 0 (0%) | NA |
| OM | 85 (70.8%) | 46 (37%) | 0.0001* |
| G I | 9 (7.5%) | 11 (8.8%) | 0.69 |
| G II | 31 (25.8%) | 21 (17%) | 0.08 |
| G III | 24 (20%) | 9 (7%) | 0.003* |
| G IV | 21 (17.5%) | 5 (4%) | 0.0006* |
| Diarrhea | 66 (55%) | 74 (59.6%) | 0.20 |
| GI | 13 (10.8%) | 3 (2.4%) | 0.007* |
| GII | 39 (32.5%) | 53 (42.7%) | 0.09 |
| GIII | 12 (10%) | 14 (11%) | 0.70 |
| GIV | 2 (1.6%) | 4 (3%) | 0.40 |
| Piles | 25 (20.8%) | 33 (26.6%) | 0.18 |
| GI | 2 (1.6%) | 3 (2.4%) | 0.60 |
| GII | 13 (10.8%) | 13 (10.4%) | 0.90 |
| GIII | 3 (2.5%) | 5 (4%) | 0.50 |
| G IV | 7 (5.8%) | 12 (9.6%) | 0.26 |
| Constipation | 26 (21.6%) | 22 (17.7%) | 0.27 |
| Renal abnormalities | 31 (25.8%) | 28 (22.5%) | 0.30 |
| GI | 12 (10%) | 8 (6.4%) | 0.30 |
| GII | 13 (10.8%) | 13 (10.4%) | 0.90 |
| GIII | 3 (2.5%) | 7 (5.5%) | 0.20 |
| GIV | 3 (2.5%) | 0 (0%) | NA |
| Hepatic dysfunction | 54 (45%) | 62 (50%) | 0.25 |
| GI | 17 (14%) | 23 (18.5%) | 0.35 |
| GII | 15 (12.5%) | 21 (17%) | 0.30 |
| GIII | 12 (10%) | 11 (8.8%) | 0.70 |
| GIV | 10 (8%) | 7 (5.5%) | 0.40 |
| Typhlitis | 13 (10.8%) | 12 (9.6%) | 0.40 |
| Febrile Neutropenia | 119 (99.1%) | 122 (98.3%) | 0.29 |
| Severe Neutropenia (G IV) | 24 (20%) | 19 (15.3%) | 0.3 |
| Invasive fungal infection | 90 (75%) | 110 (88.7%) | 0.004* |
| Viral Infection | 56 (46.6%) | 48 (38.7%) | 0.12 |
| Mean Post chemo-therapy LVEF (SD) | 61.5 (4.91) | 61.76 (4.93) | 0.70 |

[a]Using Chi square test, *Statistically significant. Dox: Doxorubicin, Ida: Idarubicin, OM: Oral mucositis, GI: Grade I, GII: Grade II, GIII: Grade III, G IV: Grade IV, LVEF: Left ventricular ejection fraction.

TLC and TLS at diagnosis of AML are considered poor prognostic factors.[8] Baseline kidney, hepatic and cardiac functions were also assessed, with no difference between the two groups.

### *Response*

There was no significant difference between the two groups, as shown in Table 2, regarding improvement, which included complete remission (CR) or partial remission (PR), or refractory disease (RD), and no difference in mortality rate at 60 days as well.

### *Treatment related toxicities*

The most common toxicities among the 2 groups were febrile neutropenia, diarrhea and vomiting. Oral mucositis (OM) was more significant in the Dox group, while the invasive fungal infection was more significant in the Ida group. Both groups revealed no cardiac toxicities. Table 3 shows the treatment related toxicities for both groups in our trial.

### *Other outcomes*

Need for parenteral nutrition was more significant in the Dox group with P value equal to 0.0019. Hospital-stay or the need for ICU admission, and the need for packed red blood cells (RBCs) or platelets (Plt) transfusion was not statistically different between the two groups, as shown in Table 4.

### *Survival analysis*

Mortality rate was 35% in Dox group, and 33% in Ida group at the end of the follow-up period. The difference was not significant. Time to remission was not significantly different as shown in Figure 1 with P value equal to 0.3594 using log-rank test.

### *Pharmacoeconomic analysis*

Figure 2 illustrates the decision tree analysis. Dox based induction treatment cost was [ (0.35 x 43871) + (0.53 x 39492) + (0.12 x 43797) ]= 39,492 L.E. Ida based induction treatment cost was [ (0.33 x 42949) + (0.49 x 44323) + (0.18 x 46791)] = 44,323 L.E. Table 5 shows the total costs per patient in the two groups for antibiotics, antifungals, TPN, G-CSF, chemotherapy, blood products, lab tests, radiological studies, hospital stay and ICU stay.

## Discussion

In cancer management systems, it has become increasingly

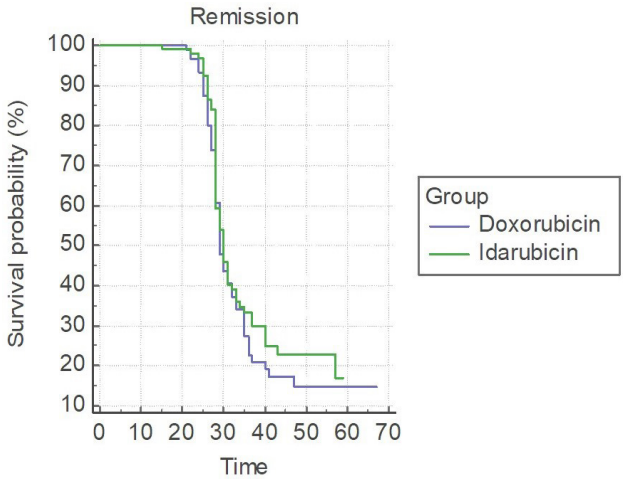


**Figure 1.** Time to Remission. No significant difference between Dox and Ida groups using log-rank test, p-value = 0.3594.

**Table 4.** Other Outcomes to Dox and Ida regimens in terms of patients' needs for TPN, blood products and hospital and ICU stay.

| Item | Dox | Ida | P value |
|---|---|---|---|
| Total number | 120 (100%) | 124 (100%) | |
| TPN | 43 (35.8%) | 23 (18.5%) | 0.0019* |
| Plt | | | |
| Mean (SD) for plt units used | 9 (5.9) | 7.9 (5.2) | 0.13 |
| Number (%) Patients who needed plt transfusion | 117 (97.5%) | 123 (99.1%) | 0.29 |
| Packed RBCs | | | |
| Mean (SD) for RBCs units used | 5.7 (3.7) | 6 (3.6) | 0.6 |
| Number (%) Patients who needed RBCs transfusion | 116 (96.6%) | 122 (98.3%) | 0.3 |
| LOS Mean (SD) days | 27 (11.45) | 27.89 (10.79) | 0.5 |
| Number of Patients admitted to ICU | 23 (19%) | 30 (24%) | 0.3 |
| Average LOS in ICU (Range) days | 3.3 (1-20) | 2.5 (1-15) | |

*Statistically significant. Dox: Doxorubicin, Ida: Idarubicin, TPN: Need for parenteral nutrition, Plt: Platelets, RBCs: Red blood cells, LOS: Length of hospital stay, SD: Standard deviation, ICU: Intensive care unit.

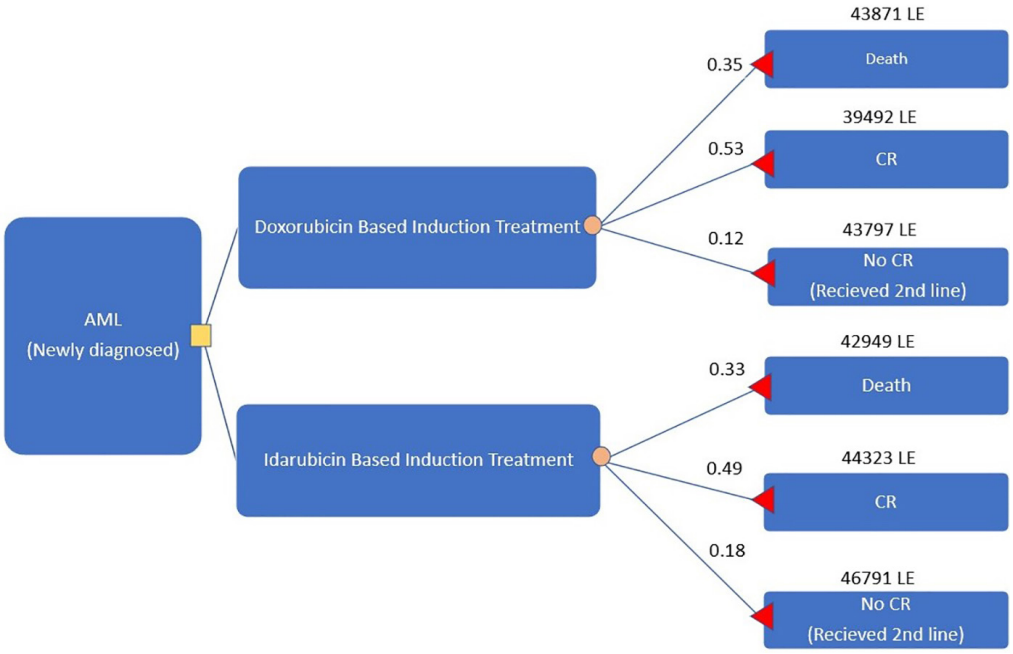


**Figure 2.** Decision Tree Analysis for Doxorubicin and Idarubicin based induction AML treatment. Patients who received Dox cost 39,492 LE to get a complete remission (CR) with probability of 0.53, while patients who received Ida cost 44,323 LE to get CR with almost same probability of 0.49. Probability of death is equal to 0.35 and 0.33 and costs 43,871 LE and 42,949 LE for Dox and Ida groups, respectively. Probability of treatment failure (no CR: no complete remission) is equal to 0.12 and 0.18 and costs 43,797 LE and 46,791 LE for Dox and Ida groups, respectively.

important to consider the financial burden introduced by new therapies. Therefore, it is important that policymakers in the oncology healthcare systems have the tools to make the best decisions about which treatment to adopt. Adopting decision-analysis is a valuable tool for making better informed decisions. In Egypt, the National Cancer Institute aims to optimize resource utilization by improving oncology patients' health and reducing cost of healthcare per patient.

The economic burden of the induction phase in AML management is a major problem. In the current study, we compared two anthracyclines used in AML treatment, Ida, the more expensive but it is the gold standard for AML management with lower CHF rates, and Dox, with the lower price, the first approved drug for AML management and the cornerstone in Egypt for AML management, but its use was hampered worldwide in AML due to its expected higher CHF rates.

To the best of our knowledge, the current prospective randomized clinical trial is the largest well conducted comparative trial and the first cost evaluation study for the two studied drugs in AML. We identified the clinical response, early mortality, toxicity profile and a pharmacoeconomic analysis for both drugs in newly diagnosed AML patients in Egypt during the induction phase of treatment.

**Table 5.** Total Costs in Dox and Ida Treatment Groups in Egyptian Pounds.

| Cost of: | Dox | Ida |
|---|---|---|
| Total number of patients | 120 | 124 |
| Cost of Antibiotics (n) | 1255680 (119) | 1619564 (122) |
| Cost of Antifungals (n) | 672960 (90) | 733336 (110) |
| Cost of TPN (n) | 108480 (43) | 71672 (23) |
| Cost of G-CSF (n) | 21960 (24) | 17484 (19) |
| Cost of Chemotherapy (n) | 94440 (120) | 541756 (124) |
| Cost of Blood products (n) | 986760 (117) | 924668 (123) |
| Cost of Lab tests (n) | 522600 (120) | 562216 (124) |
| Cost of Radiology (n) | 178800 (120) | 186496 (124) |
| Cost of Hospital stays (n) | 324840 (120) | 345836 (124) |
| Cost of ICU stay (n) | 35040 (23) | 34224 (30) |

All costs in Egyptian pounds. Dox: Doxorubicin, Ida: Idarubicin, n: number of patients with the service, TPN: total parenteral nutrition, G-CSF: growth colony stimulating factor, Chemotherapy: the cost of cytarabine plus the cost of Ida or Dox, ICU: intensive care unit, ICU stay: The total length of stay in the intensive care unit (ICU) in the hospital along the 60 days of follow up.

Our study shows that both drugs, in combination with cytarabine in the 7+3 regimen, have the same clinical effect regarding complete remission rate after one cycle of treatment This is in accordance with Bezwoda and Dansey in 1990.[11] However, Intragumtornchai *et al.*[12] in 1999, found that Ida had better CR rate compared to Dox. These two trials are the only randomized trials evaluating Ida versus Dox with a relatively small sample size. Bezwoda and Dansey, from South Africa evaluated 104 participants, using 2 cycles of 7+3 with Dox dose 30 mg/m$^2$ and 20 mg/m$^2$ orally for Ida, and no mortality, relapse rate or follow up period were reported. Intragumtornchai conducted the trial on 107 participants, using one cycle of 7+3 with 30 mg/m$^2$ for Dox and 12 mg/m$^2$ for Ida, the country, age and gender of participants, toxicity, mortality, relapse rate or follow up period were not reported. Other AML trials compared other anthracyclines, such as daunorubicin with different doses to Ida, but not Dox.[16]

In this prospective randomized trial, Dox showed the same efficacy as Ida in terms of CR, PR and treatment failure. Regarding mortality, we reported the early death rate that occurred during the induction phase within the first 60 days. Our results are in accordance with the expected 60 days mortality rates internationally, which is 38 %,[17] with no difference between the two anthracyclines. However, the significant early deaths related to AML were considered due to the early mortality from infection, hemorrhage, or hyperleukocytosis at diagnosis, that's why AML is considered an oncologic emergency.[18]

Time to remission could be used as a prognostic factor in patients with AML, as stated in previous studies.[19] Our study shows no significant difference in time to remission in both arms of the trial, which means that there would be no significant difference in prognosis for AML patients receiving either Ida or Dox.

Regarding toxicity, our study shows that both drugs have the same toxicity profile except for increasing invasive fungal infection in the Ida arm and the significant oral mucositis, especially grades III and IV, in the Dox arm and, as a result, the need for total parenteral nutrition. There was no difference in cardiotoxicity between the two groups, while Bezwoda and Dansey reported the decrease in cardiac function in four patients in the Dox group and no events in the Ida group. It may be because that they used 2 cycles with cumulative Dox dose of 180 mg/m$^2$ and we used only one cycle with cumulative Dox dose of 135 mg/m$^2$. Dox has a cumulative long-term cardiotoxicity and we focused in this study on the acute toxicities during the induction phase only. It is worth mentioning that Dox is the cornerstone in breast cancer treatment, with almost the same cumulative dose used in AML management. Breast cancer survivors live longer than AML survivors, as the 5-years relative survival for breast cancer is 90% while it is only 31% for AML.[20] Therefore, cardiotoxicity, should not be the cause to stop using Dox in AML management, as it is still used in breast cancer management.

When conducting the pharmacoeconomic analysis, from the Egyptian National Cancer Institute (NCI) perspective, we found that the Dox arm had a lower cost than the Ida arm in patients with complete remission (39,492 LE vs 44,323 LE), this is in accordance with the retrospective study by Sherif, et. al. in 2021.[10] This observational study was also performed in the Egyptian NCI on 143 patients and the results were in agreement with the current study. The main difference in cost, in the current study, is due to the chemotherapeutic and antimicrobial agents, which are higher in the Ida group, and that is because of the significantly higher invasive fungal infection incidence in the Ida group and high cost of Ida compared to Dox. The total number of patients suffering from febrile neutropenia was higher in the Ida group, while those with Grade IV febrile neutropenia requiring GCSF administration were higher in the Dox group resulting in higher GCSF cost. Although more patients in the Ida group needed blood products transfusion, more units of platelets were used for patients in the Dox group. The cost of platelets units is higher than packed RBCs (750 LE vs 250 LE). So, the total cost of blood products in Ida group, including higher packed RBCs units and lower plts units than Dox group, is lower than that in Dox group.

Despite that, Dox group has higher cost for GCSF, blood products and TPN than Ida group, Dox is still demonstrated overall lower cost.

So, our study supports the use of Dox in a limited resources setting in the light of similarity of efficacy and toxicity between Ida and Dox and the pharmacoeconomic analysis stated here.

However, the study has some limitations. The follow-up period was for a maximum of 60 days only which is short given the high relapse rate and mortality in AML patients.[1] This was also a single center and open-labelled. However, the Egyptian NCI gets patients from all-over Egypt. In addition, the decision analysis is based on the outcomes of this study alone and is lacking sensitivity analysis.

Our recommendations are to conduct a multi-center, blinded trial with long follow up period, and to conduct a sensitivity analysis in future research to explore the robustness of the findings under different scenarios and assumptions.

## Conclusion

In conclusion, our study gives another chance for doxorubicin to be a good choice for AML induction management in low- and middle-income countries, with almost same efficacy and toxicity profile compared to Idarubicin, and with a lower cost.

## Ethical Issues

The local ethics committee at Faculty of Pharmacy, Cairo University approved the protocol (CL2061), and written informed consent was obtained from all patients prior to enrollment in the study.

## Data Sharing

The data that support the findings of this study are not publicly available due to containing information that could compromise the privacy of research participants, but are available from the corresponding author upon reasonable request.

## Author Contributions

Amany El-Zeiny: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Visualization, Writing - Original Draft. Raafat Abdelfatah: Methodology, Resources, Validation, Investigation, Supervision. Maggie Abbassi: Methodology, Validation, Formal analysis, Supervision, Visualization, Writing - Review & Editing. Samar F. Farid: Validation, Formal analysis, Writing - Review & Editing, Supervision, Project administration.

## Conflict of Interest

The authors have no relevant financial or non-financial. interests to disclose.

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