Hematology/Oncology and Stem Cell Therapy

Volume 17 | Issue 1 Article 11

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ORIGINAL RESEARCH REPORT

Assessing the Efficacy of Mitoxantrone and Doxorubicin as Frontline Anthracyclines During Induction Therapy of Newly Diagnosed Acute Promyelocytic Leukemia

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Abstract

Background: **Therapeutic advances in acute promyelocytic leukemia (APL) have transformed it into today's most curable form of leukemia. However, recommended agents, including arsenic trioxide, idarubicin, or daunorubicin, are not easily available in low-middle-income countries, where outcomes remain suboptimal. We aimed to assess the efficacy and safety of more accessible anthracyclines.**

Methods: **We conducted a retrospective cohort study including sixty-one patients diagnosed with APL over a 15-year period. Patients received low-dose all-trans retinoic acid (ATRA, 25 mg/m^2) with mitoxantrone or doxorubicin as an induction to remission therapy. Groups were compared using the χ^2 and Student's t-tests. Kaplan−Meier analysis was used for survival analyses.**

Results: **Thirty (49.18%) patients received mitoxantrone, and 31 (50.82%) received doxorubicin. The median follow-up was 24.6 months (1−146). Twenty-eight (93.3%) patients achieved complete remission (CR) in the mitoxantrone group and 28 (87.1%) in the doxorubicin group ($p = 0.103$), and the median time to CR was 40 and 31 days, respectively. Mitoxantrone had a 6.7% early mortality rate and a 16.7% relapse rate compared with doxorubicin (3.2% and 32.3%, respectively). No differences were found in survival ($p = 0.795$), hospitalization days ($p = 0.261$), or adverse events ($p = 0.554$).**

Conclusions: **Using mitoxantrone or doxorubicin as induction therapy in newly diagnosed APL is a safe and adequate alternative with comparable outcomes to first-line agents in scenarios where the latter might not be readily available, such as in low-middle-income countries.**

Keywords: Acute promyelocytic leukemia, Remission induction, ATRA, Mitoxantrone, Doxorubicin

1. Introduction

Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia (AML) accounting for <10% of all AML cases in Western countries, increasing up to 38% in Latin American populations, where it is the most frequent subtype of AML [1,2]. Treatment has remarkably improved with the use of targeted agents, such as all-trans retinoic acid (ATRA) and, more recently, arsenic trioxide (ATO) with or without chemotherapy; current standard treatment for APL includes ATRA plus ATO or ATRA plus anthracycline-based chemotherapy [3,4].

Anthracycline-based chemotherapy regimens, with idarubicin alone or daunorubicin plus cytarabine, are less commonly used and approved mainly for high-risk patients [4,5]. However, due to

Received 20 July 2021; revised 29 November 2022; accepted 12 February 2023.
Available online 20 July 2023

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https://doi.org/10.56875/2589-0646.1090

the inaccessibility of ATO in Mexico, the former regimens are the current mainstay of treatment of APL [6]. Nonetheless, the cost of idarubicin hinders its use in low-to-middle-income countries. The International Consortium on Acute Promyelocytic Leukemia (IC-APL) proposed using a protocol with daunorubicin instead of idarubicin [7]; however, the availability of daunorubicin fluctuates, which further limits treatment options for APL. A previous shortage of the latter provided the opportunity to evaluate different drugs belonging to this group, such as mitoxantrone and doxorubicin [8–10].

No study has compared the efficacy of a regimen using more affordable and readily available anthracyclines during induction to remission. Therefore, we analyzed the response to treatment and survival rates of newly diagnosed patients with APL using mitoxantrone or doxorubicin as a feasible and more available option in developing countries.

2. Material and methods

We conducted an observational, longitudinal, retrospective study that included consecutive patients who fulfilled clinical and laboratory criteria for the diagnosis of APL over fifteen years from January 2005 to December 2020 and were registered in the Hematology Department at the Dr. José Eleuterio González University Hospital. The institution provides healthcare for low-income uninsured patients from the open population in Northeast Mexico. All patients provided written informed consent. The study protocol was approved by the Ethics and Research Committee of the institution and is in full compliance with the principles of the Declaration of Helsinki as revised in 2013.

The diagnosis was made morphologically and confirmed with the demonstration of PML/RARα fusion transcripts by polymerase chain reaction (PCR) or of t (15;17) by fluorescence in situ hybridization (FISH) [4]. Patients were classified by risk category, with low-to-intermediate risk patients considered those with a white blood cell count of $\leq 10 \times 10^9$/L and high-risk patients those with a leukocyte count $>10 \times 10^9$/L [4].

The decision on treatment with either mitoxantrone or doxorubicin was made based on availability at diagnosis of APL due to a shortage of the standard daunorubicin at our hematology center.

2.1. Treatment protocol

For induction therapy, the treatment protocol used was low-dose ATRA (LD-ATRA) (25 mg/m^2/d) administered until complete remission (CR) and mitoxantrone 10 mg/m^2/d or doxorubicin 45 mg/m^2/d for three consecutive days starting on day 3 until day 5. Patients with evidence of APL differentiation syndrome were treated with dexamethasone.

After hematologic recovery was observed, all patients received consolidation therapy. Treatment selection was based on drug availability at the institution, comprising three cycles of mitoxantrone (10 mg/m^2/d) or doxorubicin (45 mg/m^2/d) on days 1–3, in combination with LD-ATRA for 15 days. At the end of consolidation therapy, molecular remission was evaluated by FISH or PCR. Patients who achieved CR were given maintenance therapy for 2 years, consisting of cycles of oral mercaptopurine at 50 mg/m^2/d and methotrexate 15 mg/m^2/week on days 1–60 and ATRA 25 mg/m^2/d on days 61–75.

The decision to use low-dose ATRA was made due to financial restrictions in ATRA acquisition as an out-of-pocket cost for uninsured patients, limiting the use of higher doses for longer periods, and considering the equivalent effectiveness of low-dose compared to the standard dose of 45 mg/m^2/d [11,12].

2.2. Study endpoints

The primary endpoints for this cohort were a comparison of the proportion of CR, the median time to CR, early mortality, and toxicities between the two groups. The secondary endpoints included overall survival (OS), disease-free survival (DFS), and relapse rate. The criteria of the International Working Group were used to define hematologic and molecular CR and relapse. Early death was defined as death occurring within one month of APL diagnosis [13]. OS was defined as the time from diagnosis to death from any cause or the end of follow-up, death, or the end of follow-up, and DFS as the time from CR to relapse, death, or the end of follow-up. Toxicity analyses included the rates of neutropenic fever, infection, sepsis, mucositis (based on Common Terminology Criteria for Adverse Events, version 5.0), and in-hospital days. Infection, sepsis, and mucositis were registered according to documentation in the clinical files by physician examination or microbiological study.

2.3. Statistical analysis

Groups were compared using the χ^2 test/Fisher's exact test for categorical data and Student's t-test/Mann–Whitney U-test for quantitative data. Kaplan–Meier estimates were computed for OS, DFS. Subgroup comparisons of survival were

performed using the log-rank test. All analyses were conducted using SPSS software v.25. A P-value <0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

Sixty-five patients were diagnosed with APL from January 2005 to December 2020. Thirty patients received mitoxantrone as frontline anthracycline, and 31 received doxorubicin; the remaining four patients presented at advanced stages of the disease and died before receiving chemotherapy and were thus excluded from the comparative analysis. The median age at diagnosis for the whole cohort was 31 years (3–78), and 52.5% of the patients were men. Only nine patients (14.8%) were in the high-risk group. ATRA was initiated at a median time of 1 day (0–3) after diagnosis. Bleeding episodes occurred in 23 patients (37.7%) from the total sample, and most were of mucocutaneous origin (14/23); five patients suffered intracranial bleeding, while 4/23 presented with gastrointestinal bleeding. Table 1 shows the baseline characteristics of patients receiving each treatment.

The median follow-up for the mitoxantrone group was 24.9 months (0–67), and that for patients treated with doxorubicin was 30.9 months (0–146). At the last follow-up, no patient developed a secondary malignancy.

3.2. Response, relapse, and mortality outcomes

Differences in outcomes between the mitoxantrone and doxorubicin groups are presented in Table 2, and the survival endpoints are presented in Fig. 1. Twenty-eight patients (93.3%) achieved CR in the mitoxantrone group compared to 27 (87.1%) in the doxorubicin group (p = 0.103). No significant differences were observed in death rates between both groups; 6 patients (20%) from the mitoxantrone group died at a median time of 13 months (0–25) compared with 7 (22.6%) from the doxorubicin group at a median time of 24 months (0–119). Considering all 65 patients treated during the study period, the early death rate was 10.7%; among these patients, 3/7 died during the first week of diagnosis. The most frequent causes of death were intracranial bleeding and sepsis. A higher proportion of patients in the doxorubicin group relapsed compared to those in the mitoxantrone group; however, this difference was not significant (32.3% vs. 16.7%, p = 0.157). The median OS of the entire cohort was 24.6 months, with a two-year OS of 79.2% (CI 95%, 77.5–80.7) and a five-year OS of 66.7% (CI 95%, 65.18–68.16). No significant differences in OS rates were observed between both groups (p = 0.795). A subgroup analysis was performed according to disease severity; the two-year OS of patients with standard-risk disease was 82.6%, compared to 57.1% for those with high-risk disease (p = 0.120). The DFS for the entire cohort was 69.2% at two years (CI 95%, 67.6–70.71) and 46.7% (CI 95%, 44.7–48.6) at five years. The two-year DFS of the mitoxantrone group was 69.6% (CI 95%, 67.46–71.6), whereas that of the doxorubicin group was 61.3% (CI 95%, 58.8–63.7); no significant differences were observed (p = 0.170).

Patients who relapsed received a second course of available anthracycline and ATRA with or without cytarabine. Most patients (9/15) received ATRA plus anthracycline alone. Four patients underwent hematopoietic cell transplantation (HCT) after their first relapse; two were autologous, and two were allogeneic. A second relapse was reported in three patients; two of them received an autologous HCT, and one received an allogeneic HCT. Nine patients (60%) remained alive after relapse, with a three-year OS of 62.3%.

Table 1. Clinical features in 61 patients diagnosed with APL at a tertiary care center according to administered anthracycline.

Characteristics	All, n = 61	Mitoxantrone, n = 30	Doxorubicin, n = 31	*P-value*
Age (years)	31 (3–78)	30 (6–61)	28 (3–68)	0.571
≥50 years	8 (13.1)	5 (16.7)	3 (9.7)	0.419
Sex				
Male	32 (52.5)	13 (43.3)	19 (61.3)	0.160
Female	29 (47.5)	17 (56.7)	12 (38.7)	
Risk group (*missing, 12*)				0.130
Low-to intermediate	40 (65.6)	20 (66.7)	20 (64.5)	
High	9 (14.8)	7 (23.7)	2 (6.5)	
WBC count (x10^3/μL) median (range)	2.32 (0.36–32)	2.9 (0.81–32)	1.89 (0.36–16.9)	0.121
Platelet count (x10^3/μL) median (range)	41.4 (4–588)	41.5 (5.3–588)	41.4 (4–195)	0.208
Hb (g/dL) median (range)	9 (5.2–14.6)	9.2 (5.2–12)	8.6 (5.9–14.6)	0.747

APL = acute promyelocytic leukemia; Hb = hemoglobin; WBC = white blood cell.

Table 2. Outcomes in patients who received mitoxantrone as anthracycline compared to those who received doxorubicin during remission induction in acute promyelocytic leukemia.

Variable	Mitoxantrone, n = 30	Doxorubicin, n = 31	*P-value*
CR, n (%)	28 (93.3%)	27 (87.1)	0.103
Median time to CR, days (range)	40 (7–69)	31 (24–73)	0.719
Mortality, n (%)	6 (20)	7 (22.6)	0.806
Early death	2 (6.7)	1 (3.2)	0.534
Days hospitalized (range)	21 (8–36)	25 (11–45)	0.261
Relapse, n (%)	5 (16.7)	10 (32.3)	0.157
Second relapse	1 (3.33)	2 (6.45)	0.573
Median OS, months (range)	NR	30.9 (1–146)	0.795
Two-year OS (95% CI)	80.2% (78.0–81.2)	89.3% (88–90.3)	
Five-year OS (95% CI)	74.5% (72.1–75.7)	70.3% (67.7–72.1)	
Two-year DFS (95% CI)	69.6% (67.46–71.6)	61.3% (58.8–63.7)	0.559

CR, complete remission; OS, overall survival; DFS, disease-free survival; NR, not reached.
No differences were documented between the groups.

3.3. Toxicity analysis

Adverse events and toxicity are presented in Table 3. The incidence of treatment-related toxicities was similar between both groups (43.3% in the mitoxantrone group vs. 32.3% in the doxorubicin group, p = 0.554). The most frequent adverse event was neutropenic fever. Major toxic events included three differentiation syndromes, two in the mitoxantrone group and one in the doxorubicin group, as well as one case of cardiac failure diagnosed after the second consolidation cycle in a patient treated with doxorubicin. No significant difference in the number of in-hospital days during induction was observed between both groups (median 21 (8–36) days for mitoxantrone vs. 25 (11–45) days for doxorubicin).

4. Discussion

Two large studies in the late 90s proved the beneficial effect of combined therapy of ATRA with anthracycline-based chemotherapy for APL, causing a shift from a poor to a highly curable outcome when diagnosed early [14–16]. Nonetheless, the fluctuating availability and costs of standard anthracyclines prompted the exploration of alternative anthracyclines in our center. Patients receiving mitoxantrone and doxorubicin exhibited CR rates of 93.3% and 87.1%, respectively. Although these are higher than those reported in a Brazilian (67.9%) and a Turkish (59.2%) cohort that employed ATRA plus standard anthracycline chemotherapy [17,18], the difference in the proportion of high-risk APL must be carefully considered.

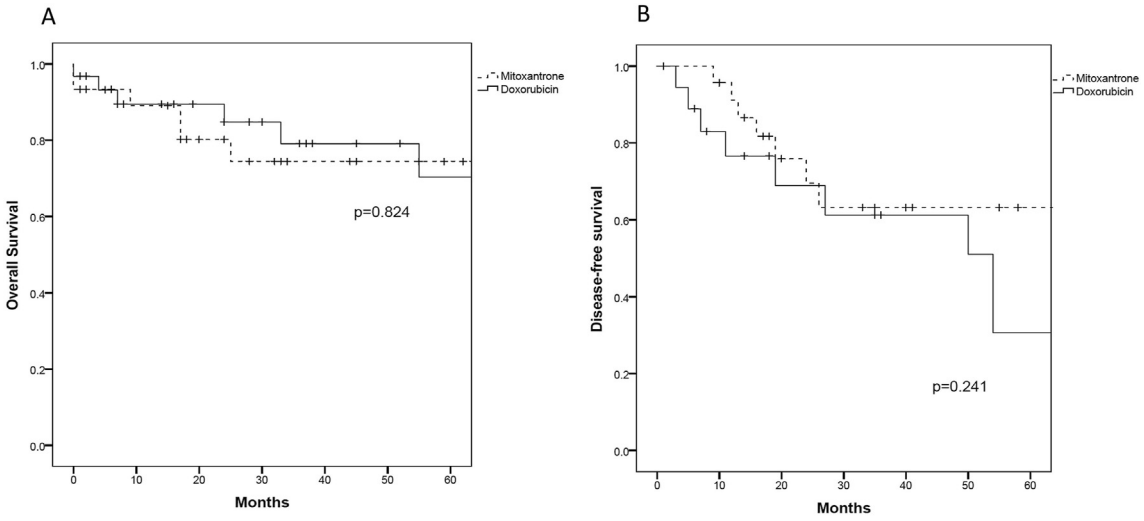

Fig. 1. Survival endpoints in patients with acute promyelocytic leukemia using mitoxantrone and doxorubicin during induction to remission at an academic referral center caring for uninsured open-population patients. Kaplan–Meier curves for (A) overall survival in patients receiving mitoxantrone and doxorubicin and (B) disease-free survival according to the type of anthracycline received.

Table 3. Treatment-related toxicities in patients in the mitoxantrone and doxorubicin groups during remission induction in acute promyelocytic leukemia.

Variable	Mitoxantrone, n (%)	Doxorubicin, n (%)	*P-value*
Number of patients	13 (43.3)	10 (32.3)	0.554
Neutropenic fever	7 (23.3)	5 (16.1)	0.479
Sepsis/Other infection	1 (3.3)	2 (6.5)	0.573
Mucositis	1 (3.3)	3 (9.7)	0.317
Pneumonia	2 (6.7)	3 (9.7)	0.668
Soft tissue abscess	3 (10)	1 (3.2)	0.285
Nausea	4 (13.3)	–	**0.035**
Phlebitis	1 (3.3)	2 (6.5)	0.573

A recent study in another Brazilian cohort with similar median age, gender, and risk distribution used daunorubicin, idarubicin, or mitoxantrone plus ATRA as induction therapy, demonstrating a CR rate of 87.8% (95% CI, 81.8–93.8), comparable to the present study [19]. However, no comparison of CR rates between different anthracyclines was conducted in that study. A cohort of 20 patients with mostly intermediate-risk APL that received standard anthracycline chemotherapy plus ATRA as induction therapy in another referral center in Mexico demonstrated a CR rate of 94.4%, an outcome comparable to our study [20]. Survival analyses in the present study yielded similar OS rates to those of the previously mentioned studies. These outcomes might suggest the potential use of alternative anthracyclines in situations where costs and unavailability restrict the use of standard chemotherapeutic agents, especially in low-to-intermediate risk patients.

Early death remains a major issue in APL treatment. We documented a rate of 10.7% in the total cohort, similar to those reported in industrialized countries, ranging from 5 to 10% [21–23] to 17% in the United States [24], and considerably lower than 26–30% observed in Pakistani, Swedish, Brazilian, and Indian populations [5,17,25,26]. Importantly, more than half of the patients with early mortality in our study did not receive chemotherapy due to delayed presentation to the hospital, which has been reported as a contributing factor for outcomes of APL in low-income groups [17]. No differences in mortality rates were observed between the mitoxantrone and doxorubicin groups; 13 patients (21.3%) died at the last follow-up. This rate was congruent with the one observed in a recently published Brazilian cohort (22.7%) [19].

We observed a considerably higher relapse rate (24.5%) than other studies (2.2–5.5%) [7,17,20,26]. Nonetheless, a comparable relapse rate to that of the Brazilian cohort was observed (24.5% vs. 22%). We hypothesize that the high rate in our cohort might be attributed to poor adherence during maintenance due to financial restrictions in ATRA acquisition as an out-of-pocket cost for uninsured patients, which further limits the use of standard high doses for longer periods, such as during maintenance therapy. Considering that the cost of 100 capsules of 10 mg of ATRA is approximately 850 USD, and the standard dosage (45 mg/m^2/day) is almost twice that of the low-dose regimen (25 mg/m^2/day), treatment costs can substantially increase depending on the therapeutic scheme, patient's physique, and time to response. This represents a considerable cost for our open-population uninsured patients paying out of pocket for their treatment; the monthly family income in this group is approximately 800 USD. Relapse rates from 27% up to 40% have been reported with low-dose ATRA in middle-income countries [27–29], compared to 6% with standard-dose ATRA [13,30]. We observed non-significantly higher relapse rates in the doxorubicin group (32.3% vs. 16.7%). The results of a study published in 2015 with the same population also favor the use of mitoxantrone; there was a relapse rate of 52.8% with doxorubicin compared to 31.3% with mitoxantrone ($p = 0.07$), while the OS was similar to that of the present study [8]. Additionally, as doxorubicin has greater cardiotoxicity, with left ventricular diastolic dysfunction generally observed with cumulative doses greater than 200 mg/m^2 [31], mitoxantrone is a more appealing option [32]. The response to treatment and survival rates in our cohort compared to that in different regimens are shown in Table 4. A recent study in Mexico analyzed the cost of the modified IC-APL protocol using ATRA + daunorubicin and compared it with that of the standard protocol of ATRA + ATO used in the USA, Italy, and Canada [33]. The induction phase using the former protocol regimen costs approximately $3,782, compared to $20,503 and $8234 using the latter regimen in USA and Italy, respectively. Using LD-ATRA further lowers the potential costs, highlighting the economic difference between regimens.

Table 4. Overview of induction to remission treatment in patients newly diagnosed with acute promyelocytic leukemia described in the literature and those in the present report.

Reference	Induction Treatment	Sample characteristics	Response to treatment	Survival outcomes
Lo-Coco et al., 2013 [3]	ATO 0.15 mg/kg/day + ATRA 45 mg/m^2/day	n = 77 Low-to-intermediate risk patients Age: 44 (19–70) Follow-up: 34.4 months	CR: 100% Days to CR: 32 Relapse: 2.5%	2-year OS: 99% DFS: 97%
Lo-Coco et al., 2013 [3]	ATRA 45 mg/m^2/day+ Idarubicin 12 mg/m^2/day	n = 79 Low-to-intermediate risk patients Age: 46 (18–70) Follow-up: 34.4 months	CR: 95% Days to CR: 35 ED: 5% Relapse: 6.6%	2-year OS: 91% DFS: 90%
Rego et al., 2016 [7]	ATRA 45 mg/m^2/day + Daunorubicin 60 mg/m^2/day	n = 180 Low-to-intermediate risk: 68% High risk: 32% Age: 34 (15–73) Follow-up: 28 months	CR: 85% Days to CR: 38 ED: 25% Relapse: 6%	2-year OS: 80% DFS: 91%
Powell et al., 2016 [34]	ATRA 45 mg/m^2/day + Cytarabine 200 mg/m^2 + Daunorubicin 50 mg/m^2	n = 481 Low-to-intermediate risk: 76.5% High risk: 23.4% Age: (15–79) Follow-up: 54 months	CR: 90% ED: 8% Relapse: 4%	3-year OS: 81–86% DFS: 70–90%
Crespo-Solis et al., 2016 [20]	ATRA 45 mg/m^2/day + Daunorubicin 60 mg/m^2/day	n = 18 Low-to-intermediate risk: 83.4% High risk: 16.6% Age: 40 (21–74) Follow-up: 29 months	CR: 94.4% Days to CR: 42 (34–158) ED: 5.5% Relapse: 5.5%	2- year OS: 89.1% DFS: 89.1%
Shaikh et al., 2020 [26]	ATRA 45 mg/m^2/day + Daunorubicin or Idarubicin ± Cytarabine	n = 40 Low-to-intermediate risk: 59.09% High risk: 36.3% Age: 34 (17–60) Follow-up: 42 months	CR: NR Days to CR: NR ED: 30% Relapse: 2.5%	2-year OS: 80% DFS: 80%
Steffenello-Durigon et al., 2021 [19]	ATRA 45 mg/m^2/day + Daunorubicin or Idarubicin or Mitoxantrone ± Cytarabine 1000 mg/m^2	n = 44 Low-to-intermediate risk: 75% High risk: 25% Age: 34 (15–58) Follow-up: 150 months	CR: 87.8% Days to CR: NR ED: 15.9% Relapse: 22%	2-year OS: 80% 5-year DFS: 62%
Jaime-Pérez et al., 2023	ATRA 25 mg/m^2/d+ Mitoxantrone 10 mg/m^2/d	n = 30 Low-to-intermediate risk: 67% High risk: 24% Age: 30 (6–61) Follow-up: 24.6 months	CR: 93.3% Days to CR: 40 ED: 6.7% Relapse: 16.6%	2-year OS: 79.7% DFS: 69.6%
Jaime-Pérez et al., 2023	ATRA 25 mg/m^2/d+ Doxorubicin 45 mg/m^2/d	n = 31 Low-to-intermediate risk: 64.5% High risk: 6.5% Age: 28 (3–68) Follow-up: 24.6 months	CR: 87.1% Days to CR: 31 ED: 3.2% Relapse: 32.3%	2-year OS: 89.3% DFS: 61.3%

ATO, arsenic trioxide; ATRA, all-trans retinoic acid; CR, complete remission; ED, early death; OS, overall survival; DFS, disease-free survival; CIR, cumulative incidence of relapse; NR, not reached.

The main limitations of this study are its retrospective nature and the use of ATRA at lower doses, which could act as a confounding factor when comparing the efficiency of different ANTs. The relatively small sample size and the length of follow-up also limit definitive conclusions.

The study's strengths are the balanced number of patients in each group and that the study was conducted at a single institution over an extended period. It involved the same team of specialists, and the standards of care were uniform throughout the 15 years.

5. Conclusion

To our knowledge, the frontline use of mitoxantrone and doxorubicin has not been previously reported in APL. In this study, we demonstrated that these agents are feasible alternatives for APL induction treatment, with comparable response rates and survival outcomes reported with the use of classical ANTs, idarubicin, and daunorubicin. Both anthracyclines used exhibited a similar safety and efficacy profile. Although chemotherapy-based regimens are rarely used to manage APL, our results contribute to solving a significant challenge in APL treatment concerning minimizing disparities in outcomes in developing countries where the availability of standard agents, such as ATO or daunorubicin, is limited. In these circumstances, the use and accessibility of mitoxantrone or doxorubicin offer an acceptable and affordable option for patients needing treatment for this highly curable form of acute leukemia.

Availability of data and material

The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by José Carlos Jaime-Pérez, Eugenia M. Ramos-Dávila, and Jesús D. Meléndez-Flores. The first draft of the manuscript was written by Eugenia M. Ramos-Dávila, José Carlos Jaime-Pérez, Jesús D. Meléndez-Flores, Mariana González-Treviño, and David Gómez-Almaguer. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Acknowledgments

We thank Sergio Lozano-Rodriguez, MD, for his critical review of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics approval

The protocol of the study was approved by the Ethics and Research Committee of the institution and is in full compliance with the principles of the Declaration of Helsinki as revised in 2013.

References

[1] Sant M, Allemani C, Tereanu C, De Angelis R, Capocaccia R, Visser O, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood 2010;116:3724–34. https://doi.org/10.1182/blood-2010-05-282632.

[2] Gómez-Almaguer D, Marcos-Ramírez ER, Montaño-Figueroa EH, Ruiz-Argüelles GJ, Best-Aguilera CR, López-Sánchez M del C, et al. Acute Leukemia Characteristics are Different Around the World: the Mexican Perspective. Clin Lymphoma, Myeloma & Leukemia 2017;17:46–51. https://doi.org/10.1016/j.clml.2016.09.003.

[3] Lo-Coco F, Avvisati G, Vignetti M, Thiede C, Orlando SM, Iacobelli S, et al. Retinoic Acid and Arsenic Trioxide for Acute Promyelocytic Leukemia. N Engl J Med 2013;369:111–21. https://doi.org/10.1056/NEJMoa1300874.

[4] Sanz MA, Fenaux P, Tallman MS, Estey EH, Löwenberg B, Naoe T, et al. Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet. Blood 2019;133:1630–43. https://doi.org/10.1182/blood-2019-01-894980.

[5] Danthala M, Golamari KR, Seshachalam A, Mikkilineni A, Chappidi S, Mekala MB, et al. Walking a Tightrope: Dosage Modifications and Treatment Outcomes of All- Trans -Retinoic Acid, Arsenic Trioxide, and Daunorubicin for High-Risk Acute Promyelocytic Leukemia. JCO Glob Oncol 2020:1749. https://doi.org/10.1200/GO.20.00226. –56.

[6] Zapata-Canto N, Aguilar M, Arana L, Montano E, Ramos-Penafiel C, De la Pena JA, et al. Acute Promyelocytic Leukemia: A Long-Term Retrospective Study in Mexico. J Hematol 2021;10:53–63. https://doi.org/10.14740/jh773.

[7] Rego EM, Kim HT, Ruiz-Argüelles GJ, Undurraga MS, Uriarte M del R, Jacomo RH, et al. Improving acute promyelocytic leukemia (APL) outcome in developing countries through networking, results of the International Consortium on APL. Blood 2013;121:1935–43. https://doi.org/10.1182/blood-2012-08-449918.

[8] Jaime-Perez JC, Colunga-Pedraza PR, Gutiérrez-Aguirre CH, Pinzón-Uresti MA, Cantú-Rodríguez OG, Herrera-Garza JL, et al. Efficacy of mitoxantrone as frontline anthracycline during induction therapy in adults with newly diagnosed

acute lymphoblastic leukemia: a single-center experience. Leuk Lymphoma 2015;56:2524–8. https://doi.org/10.3109/10428194.2015.1009058.
[9] Patel S, Liedtke M, Ngo D, Medeiros BC. A single-center experience of the nationwide daunorubicin shortage: substitution with doxorubicin in adult acute lymphoblastic leukemia. Leuk Lymphoma 2013;54:2231–5. https://doi.org/10.3109/10428194.2013.772606.
[10] Nickel RS, Keller F, Bergsagel J, Cooper T, Daves M, Sabnis H, et al. Mitoxantrone as a substitute for daunorubicin during induction in newly diagnosed lymphoblastic leukemia and lymphoma. Pediatr Blood Cancer 2014;61:810–4. https://doi.org/10.1002/pbc.24892.
[11] Castaigne S, Lefebvre P, Chomienne C, Suc E, Rigal-Huguet F, Gardin C, et al. Effectiveness and pharmacokinetics of low-dose all-trans retinoic acid (25 mg/m2) in acute promyelocytic leukemia. Blood 1993;82:3560–3.
[12] Chen GQ, Shen ZX, Wu F, Han JY, Miao JM, Zhong HJ, et al. Pharmacokinetics and efficacy of low-dose all-trans retinoic acid in the treatment of acute promyelocytic leukemia. Leukemia 1996;10:825–8.
[13] Mantha S, Goldman DA, Devlin SM, Lee J-W, Zannino D, Collins M, et al. Determinants of fatal bleeding during induction therapy for acute promyelocytic leukemia in the ATRA era. Blood 2017;129:1763–7. https://doi.org/10.1182/blood-2016-10-747170.
[14] Avvisati G, Lo Coco F, Diverio D, Falda M, Ferrara F, Lazzarino M, et al. AIDA (all-trans retinoic acid + idarubicin) in newly diagnosed acute promyelocytic leukemia: a Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) pilot study. Blood 1996;88:1390–8.
[15] Fenaux P, Chastang C, Chevret S, Sanz M, Dombret H, Archimbaud E, et al. A randomized comparison of all transretinoic acid (ATRA) followed by chemotherapy and ATRA plus chemotherapy and the role of maintenance therapy in newly diagnosed acute promyelocytic leukemia. The European APL Group. Blood 1999;94:1192–200.
[16] Wang Z-Y, Chen Z. Acute promyelocytic leukemia: from highly fatal to highly curable. Blood 2008;111:2505–15. https://doi.org/10.1182/blood-2007-07-102798.
[17] Jacomo RH, Melo RAM, Souto FR, de Mattos ER, de Oliveira CT, Fagundes EM, et al. Clinical features and outcomes of 134 Brazilians with acute promyelocytic leukemia who received ATRA and anthracyclines. Haematologica 2007;92:1431–2. https://doi.org/10.3324/haematol.10874.
[18] Serefhanoglu S, Buyukasik Y, Goker H, Sayinalp N, Haznedaroglu IC, Aksu S, et al. Clinical features and outcomes of 49 Turkish patients with acute promyelocytic leukemia who received ATRA and anthracyclines (PETHEMA protocol) therapy. Leuk Res 2010;34:e317–9. https://doi.org/10.1016/j.leukres.2010.07.027.
[19] Steffenello-Durigon G, Bigolin A, Moraes ACR de, Rudolf-Oliveira RC, Moral JAG Del, Santos-Silva MC. Follow-up and outcome of the twelve-year experience in adult patients with acute promyelocytic leukemia. Hematol Transfus Cell Ther 2021;43:21–7. https://doi.org/10.1016/j.htct.2019.12.001.
[20] Crespo-Solis E, Contreras-Cisneros J, Demichelis-Gómez R, Rosas-López A, Vera-Zertuche JM, Aguayo A, et al. Survival and treatment response in adults with acute promyelocytic leukemia treated with a modified International Consortium on Acute Promyelocytic Leukemia protocol. Rev Bras Hematol Hemoter 2016;38:285–90. https://doi.org/10.1016/j.bjhh.2016.08.002.
[21] Avvisati G, Lo-Coco F, Paoloni FP, Petti MC, Diverio D, Vignetti M, et al. AIDA 0493 protocol for newly diagnosed acute promyelocytic leukemia: very long-term results and role of maintenance. Blood 2011;117:4716–25. https://doi.org/10.1182/blood-2010-08-302950.
[22] Adès L, Guerci A, Raffoux E, Sanz M, Chevallier P, Lapusan S, et al. Very long-term outcome of acute promyelocytic leukemia after treatment with all-trans retinoic acid and chemotherapy: the European APL Group experience. Blood 2010;115:1690–6. https://doi.org/10.1182/blood-2009-07-233387.
[23] de la Serna J, Montesinos P, Vellenga E, Rayón C, Parody R, León A, et al. Causes and prognostic factors of remission induction failure in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and idarubicin. Blood 2008;111:3395–402. https://doi.org/10.1182/blood-2007-07-100669.
[24] Park JH, Qiao B, Panageas KS, Schymura MJ, Jurcic JG, Rosenblat TL, et al. Early death rate in acute promyelocytic leukemia remains high despite all-trans retinoic acid. Blood 2011;118:1248–54. https://doi.org/10.1182/blood-2011-04-346437.
[25] Lehmann S, Ravn A, Carlsson L, Antunovic P, Deneberg S, Möllgård L, et al. Continuing high early death rate in acute promyelocytic leukemia: a population-based report from the Swedish Adult Acute Leukemia Registry. Leukemia 2011;25:1128–34. https://doi.org/10.1038/leu.2011.78.
[26] Shaikh MU, Ali N, Karim F, Raheem A, Sarwar S. Improved outcome in early induction deaths in patients with acute promyelocytic leukemia after therapeutic and supportive interventions: a follow up study of seven-years' experience at a tertiary care center. Am J Blood Res 2020;10:82–9.
[27] Jaime-Pérez JC, González-Leal XJ, Pinzón-Uresti MA, Gómez-De León A, Cantú-Rodríguez OG, Gutiérrez-Aguirre H, et al. Is There Still a Role for Low-Dose All-Transretinoic Acid in the Treatment of Acute Promyelocytic Leukemia in the Arsenic Trioxide Era? Clin Lymphoma, Myeloma & Leukemia 2015;15:816–9. https://doi.org/10.1016/j.clml.2015.09.002.
[28] Lou Y, Qian W, Meng H, Mai W, Tong H, Tong Y, et al. Long-term efficacy of low-dose all-trans retinoic acid plus minimal chemotherapy induction followed by the addition of intravenous arsenic trioxide post-remission therapy in newly diagnosed acute promyelocytic leukaemia. Hematol Oncol 2014;32:40–6. https://doi.org/10.1002/hon.2076.
[29] Ramos-Blas G, López-Karpovitch X, Crespo-Solís E, Aguayo A. Dosis baja de ácido transretinoico en adultos con leucemia promielocítica aguda. Gac Med Mex 2013;149:265–71.
[30] Thomas X. Acute Promyelocytic Leukemia: A History over 60 Years—From the Most Malignant to the most Curable Form of Acute Leukemia. Oncol Ther 2019;7:33–65. https://doi.org/10.1007/s40487-018-0091-5.
[31] Barbosa RR, Bourguignon TB, Torres LD, Arruda LS, Jacques T de M, Serpa RG, et al. Anthracycline-associated cardiotoxicity in adults: systematic review on the cardioprotective role of beta-blockers. Rev Assoc Med Bras 2018;64:745–54. https://doi.org/10.1590/1806-9282.64.08.745.
[32] Posner L, Dukart G, Goldberg J, Bernstein T, Cartwright K. Mitoxantrone: an overview of safety and toxicity. Invest N Drugs 1985;3. https://doi.org/10.1007/BF00174159.
[33] Rodríguez-Rodríguez S, Guerrero-Torres L, Díaz-Huízar MJ, Pomerantz A, Ortíz-Vilchis M del P, Demichelis-Gómez R. Cost-effectiveness of the regimen proposed by the International Consortium on Acute Promyelocytic Leukemia for the treatment of newly diagnosed patients with Acute Promyelocytic Leukemia. Hematol Transfus Cell Ther 2021;43:476–81. https://doi.org/10.1016/j.htct.2020.08.013.
[34] Powell BL, Moser B, Stock W, Gallagher RE, Willman CL, Stone RM, et al. Arsenic trioxide improves event-free and overall survival for adults with acute promyelocytic leukemia: North American Leukemia Intergroup Study C9710. Blood 2010;116:3751–7. https://doi.org/10.1182/blood-2010-02-269621.