Acute Promyelocytic Leukemia: A Long-Term Retrospective Study in Mexico

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Abstract

Background: The present retrospective study reviewed acute promyelocytic leukemia (APL) cases recorded in Mexico between January 2007 and January 2017. The primary objective of the study was to evaluate overall survival (OS) in Mexican patients with APL. Secondary objective was to evaluate the impact of induction treatment with different anthracyclines on OS, event-free survival (EFS) and complications in this patient population.

Methods: The medical charts of patients referred to medical institutions in Mexico from January 2007 through January 2017 for the treatment of suspected APL were reviewed retrospectively. Patients aged 15 - 75 years, in whom the diagnosis of APL was confirmed, were included in the study. Study participants received induction and consolidation treatment with ATRA plus either daunorubicin or idarubicin, followed by 2 years of single-agent ATRA as maintenance therapy. Patients who were unable to pay for ATRA treatment received anthracycline-based induction and consolidation, with methotrexate plus mercaptopurine as maintenance therapy.

Results: A total of 360 patients from 21 public and private hospitals were included in the study. The median age of the population was 37 years, and 51% were male. Of the 360 patients, 205 (57%) vs. 155 (43%) received daunorubicin vs. idarubicin as induction treatment for APL. ATRA was administered to 201 (98%) patients in the daunorubicin group vs. 138 (89%) in the idarubicin group (P = 0.001), and was initiated at diagnosis in 92% vs. 73% of recipients, respectively (P = 0.0001). At 150 months, OS and EFS for the entire population were 84% and 79%, respectively. Both OS (90% vs. 76%, P = 0.003) and EFS (85% vs. 72%, P = 0.001) were significantly prolonged in daunorubicin vs. idarubicin recipients. Rates of complications were similar in the two groups.

Conclusions: As arsenic trioxide (ATO) is not currently available in Mexico, anthracycline plus ATRA is the mainstay of treatment for APL here. Our results confirm the efficacy of this strategy, with high OS and EFS rates being observed 12.5 years after diagnosis.

Keywords: Acute promyelocytic leukemia; Mexico; Retrospective study; ATRA; Daunorubicin; Idarubicin; Anthracycline
Introduction

Acute promyelocytic leukemia (APL) is a distinctive subtype of acute myeloid leukemia (AML) that is characterized by specific biological and clinical findings. These include: bone marrow infiltration by atypical promyelocytes [1-3]; a balanced reciprocal translocation between chromosomes 15 and 17 (t(15;17)), which fuses the promyelocyte (PML) gene on chromosome 15 to the retinoic acid receptor alfa (RAR-alfa) on chromosome 17 [2, 4, 5]; and coagulopathy associated with a severe hemorrhagic diathesis [5, 6]. The coagulopathy associated with APL is complex and incorporates several processes, including disseminated intravascular coagulation (DIC), fibrinolysis and proteolysis [7]. It is potentially life-threatening and, while typically present at diagnosis, is worsened by the initiation of chemotherapy [1, 5, 8].

There are two main morphological variants of APL: a hypergranular variant, with cells that typically contain bundles of Auer rods and have a reniform or bilobed nucleus [5, 9]; and a microgranular form, in which Auer rods are less common and no granules are visible on light microscopy [5, 10]. The hypergranular variant is the more common, representing around 75-79% of cases [10, 11]. In a typical APL case, abnormal promyelocytes constitute at least 30% of the myeloid cells in a bone marrow sample [2], and staining with myeloperoxidase is strongly positive [12].

In the United States [13] and in Europe [14], arsenic trioxide (ATO) is approved in combination with all-trans retinoic acid (ATRA) for the treatment of newly diagnosed patients with low-to-intermediate risk APL (white blood cell (WBC) count ≤ 10 × 10⁹/L). In cases where ATO is either contraindicated or unavailable, the National Comprehensive Cancer Network (NCCN) recommends induction treatment with an anthracycline plus ATRA [15]. As ATO is not currently reimbursed in Mexico as a front-line treatment for APL, anthracyclines are the cornerstone of induction and consolidation regimens here, with ATRA being added when possible. The present study aimed to evaluate survival in Mexican patients with APL, and the impact of different anthracyclines on both survival rates and complications in this population. The study is registered with ClinicalTrials.gov identifier NCT04562818.

Materials and Methods

Patients

Patients aged 15 - 75 years, who were treated for APL at one of 21 hospitals in Mexico between January 2007 and January 2017, were eligible for inclusion. The diagnosis of APL was confirmed by the detection of abnormal promyelocytes in bone marrow samples and verification of the t(15;17) chromosomal translocation either by karyotyping or by reverse transcriptase polymerase chain reaction (RT-PCR) identification of the APL-specific genetic lesion. Additional study inclusion criteria were: Eastern Cooperative Oncology Group (ECOG) performance status of 0 - 2; and eligibility for combination treatment with intensive chemotherapy plus ATRA.

Study design and treatments

This was a retrospective, multicenter, longitudinal study. Consistent with standard medical practice in Mexico, patients received: one cycle of anthracycline and ATRA-based induction treatment; three cycles of anthracycline and ATRA-based consolidation; and single-agent ATRA as maintenance therapy for 2 years. In patients with WBC ≤ 10 × 10⁹/L, induction treatment comprised either idarubicin 12 mg/m² or daunorubicin 60 mg/m² on days 2, 4, 6, and 8 of a 28-day cycle, plus ATRA 45 mg/m² daily in divided doses. Patients with WBC > 10 × 10⁹/L received the same induction regimen, but with cytarabine 100 mg/m² being added on seven consecutive days in each 28-day cycle. Patients who were unable to pay for ATRA treatment received anthracycline-based induction and consolidation without ATRA, and methotrexate plus mercaptopurine as maintenance therapy. In addition to the above treatments, all patients received intrathecal methotrexate 12 mg as central nervous system prophylaxis. Patients with WBC ≤ 10 × 10⁹/L received three cycles of prophylaxis, while those with WBC > 10 × 10⁹/L received six cycles.

Ethical issues

In accordance with the Declaration of Helsinki, all patients provided written informed consent prior to receiving chemotherapy. The study was approved by the investigational committee of the National Institute of Oncology, Mexico.

Study objectives

The primary objective of the study was to evaluate OS in Mexican patients with APL. Secondary objective was to evaluate OS, event-free survival (EFS) and complications in this population following daunorubicin- vs. idarubicin-based induction treatment plus 2 years of maintenance therapy.

Study assessments and definitions

OS was defined as the time from diagnosis of APL to death from any cause. EFS was defined as the time from diagnosis of APL to the first occurrence of an event, where an event was defined as: failure to achieve a complete response (CR), as demonstrated by continued detection of the PML-RAR-alfa fusion gene on PCR analysis; disease relapse after prior achievement of a CR; or death. Treatment response was assessed by complete blood count (CBC) after the first month of induction, and subsequently by CBC monthly during consolidation and every 3 months during the maintenance phase. CR was defined as the achievement of a normalized CBC and PML-RAR-alfa transcript level below the PCR detection limit. Disease relapse was defined as CBC evidence of pancytopenia in combination with intensive chemotherapy plus ATRA.
with PCR detection of the PML-RAR-alfa fusion gene in a patient with a previously confirmed CR. High-risk APL was defined as WBC count $>10 \times 10^9/L$; intermediate-risk APL as WBC count $\leq 10 \times 10^9/L$ and platelet count $\leq 40 \times 10^9/L$; and low-risk APL as WBC count $\leq 10 \times 10^9/L$ and platelet count $> 40 \times 10^9/L$. Early death was defined as death within 30 days of APL diagnosis.

**Statistical methods**

Nominal variables were expressed as percentages and compared using a Chi-squared test. Numerical variables were presented as mean and median values, with minima, maxima and standard deviations as appropriate for handling the described variable. Numerical variables were compared using Student’s t-test or analysis of variance (ANOVA). Non-parametric tests (Kruskal-Wallis or Mann-Whitney) were used for multivariate analyses. Survival analyses were conducted using Kaplan-Meier methodology. P was considered statistically significant at a value of $< 0.05$.

**Results**

**Patients and treatments**

A total of 360 patients were eligible for inclusion in the study. The median age of the population was 37 years. Seventy-six (21.1%) of the 360 patients presented with hemorrhage, and 112 (31.1%) had DIC at diagnosis. Diabetes was the most common comorbidity, being reported in 35 (9.7%) patients. A total of 136 (37.8%) patients were categorized as low risk, 81 (22.5%) as intermediate risk and 143 (39.7%) as high risk. Patient demographics and disease characteristics at diagnosis are summarized in Table 1.

Two hundred five (56.9%) patients received daunorubicin as induction treatment, while 155 (43.1%) patients received idarubicin. The choice of anthracycline was determined by availability at the treating institution. A total of 339 (94.2%) patients received ATRA in addition to an anthracycline as induction therapy: 201 (98.0%) in the daunorubicin group and 138 (89.0%) in the idarubicin group ($P = 0.001$) (Table 2). Among patients who received ATRA, initiation of ATRA treatment at diagnosis was significantly more common in the daunorubicin group vs. the idarubicin group (91.5% vs. 72.5%; $P = 0.0001$). The median duration of induction and consolidation therapy with ATRA was 75 days for the entire population, and did not differ significantly by anthracycline (73 days in the daunorubicin group vs. 77 days in the idarubicin group; $P = 0.41$) (Table 2).

**Efficacy**

**Treatment response**

Overall, 310 patients achieved a CR following induction treatment: 187 (91.2%) patients in the daunorubicin group vs. 123 (79.4%) patients in the idarubicin group ($P = 0.04$) (Table 2). Disease relapse occurred in similar numbers of patients in the two anthracycline groups: 12 (6%) daunorubicin patients vs. 11 (7%) idarubicin patients ($P = 0.32$).

**Survival**

After a median follow-up of 150 months, OS was 83.6% in the total population (Fig. 1a), and was significantly prolonged in the daunorubicin group vs. the idarubicin group (89.8% vs 75.5%, $P = 0.003$; Fig. 1b). EFS for the total population was 79.2% (Fig. 2a). Similar to OS, EFS was significantly prolonged in the daunorubicin group vs. the idarubicin group (84.9% vs. 71.6%, $P = 0.001$; Fig. 2b).

Fifty (13.9%) early deaths were reported: 18 (8.8%) among patients treated with daunorubicin vs. 32 (20.6%) in the idarubicin group ($P = 0.001$). All early deaths were attributed to either DIC (33 patients: 10 in the daunorubicin group and 23 in the idarubicin group, $P = 0.002$) or infection (17 patients: eight patients treated with daunorubicin and nine treated with idarubicin, $P = 0.250$).

**Uni- and multivariate analyses**

Uni- and multivariate analyses identified age, risk category at diagnosis, the type of anthracycline used, ATRA treatment and the timing of its initiation, and DIC as significant prognostic factors for OS (Table 3). No significant association was found between differentiation syndrome (DS) and OS.

**Complications**

While receiving induction treatment, 336 (93.3%) and 66 (18.3%) patients developed febrile neutropenia (FN) and DS, respectively (Table 4). FN was treated with ceftazidime/amikacin, imipenem, or levofloxacin. Similar rates of both FN (94.1% vs. 92.3%; $P = 0.44$) and DS (16.1% vs. 21.3%; $P = 0.22$) were reported among patients treated with daunorubicin vs. idarubicin (Table 4). Ceftazidime/amikacin was prescribed for similar percentages of patients with FN in the two anthracycline groups (42.9% daunorubicin vs. 46.5% idarubicin). However, 29.8% and 21.5% of patients in the daunorubicin group who presented with FN received imipenem and levofloxacin, respectively, compared with 40.6% and 5.2% of patients with FN in the idarubicin group.

**Discussion**

APL is a medical emergency that requires prompt diagnosis and management, and effective monitoring of measurable residual disease (MRD) [5, 6]. For many years, APL was associated with high rates of bleeding complications and early death [2, 16-20]. The first major breakthrough in its treatment
Table 1. Patient Demographics and Disease Characteristics at Diagnosis

| Characteristics                      | All patients (N = 360) | Daunorubicin recipients (n = 205) | Idarubicin recipients (n = 155) | \( P \)  \\
|--------------------------------------|------------------------|-----------------------------------|---------------------------------|---------  \\
| Median age, years (range)            | 37 (15 - 73)           | 36 (15 - 73)                      | 35 (16 - 67)                    | 0.65  \\
| Male sex, n (%)                      | 182 (50.6)             | 110 (53.7)                        | 72 (46.5)                       | 0.202  \\
| Hemorrhage, n (%)                    | 76 (21.1)              | 39 (19.0)                         | 37 (23.9)                       | 0.49  \\
| CNS                                  | 8 (2.2)                | 5 (2.4)                           | 3 (1.9)                         | 0.39  \\
| Digestive system                     | 18 (5.0)               | 8 (3.9)                           | 10 (6.5)                        | 0.41  \\
| Genitourinary system                 | 15 (4.2)               | 7 (3.4)                           | 8 (5.2)                         | 0.50  \\
| Integumentary system                 | 35 (9.7)               | 15 (7.3)                          | 20 (12.9)                       | 0.44  \\
| DIC, n (%)                           | 112 (31.1)             | 43 (21.0)                         | 71 (45.8)                       | 0.02  \\
| Infection, n (%)                     | 44 (12.2)              | 21 (10.2)                         | 23 (14.8)                       | 0.48  \\
| Comorbidities, n (%)                 | 46 (12.8)              | 23 (11.2)                         | 23 (14.8)                       | NA    \\
| Arterial hypertension                | 7 (1.9)                | 4 (2.0)                           | 3 (1.9)                         |       \\
| Asthma/COPD                           | 1 (0.3)                | 0 (0.0)                           | 1 (0.6)                         |       \\
| Chronic renal disease                | 1 (0.3)                | 0 (0.0)                           | 1 (0.6)                         |       \\
| Collagenopathy                       | 2 (0.6)                | 1 (0.5)                           | 1 (0.6)                         |       \\
| Diabetes mellitus                    | 35 (9.7)               | 18 (8.8)                          | 17 (11.0)                       |       \\
| Laboratory parameters, median (range)|                       |                                   |                                 |        \\
| Leukocytes, per µL                   | 22 (1 - 450)           | 6.2 (2 - 434)                     | 8.0 (1 - 450)                   | 0.34  \\
| Hematocrit, %                        | 24 (10 - 42)           | 25 (11 - 42)                      | 22 (10 - 41)                    | 0.50  \\
| Platelets, per µL                    | 40 (2 - 318)           | 40 (3 - 118)                      | 38 (2 - 315)                    | 0.18  \\
| Partial thromboplastin time, s       | 32 (18 - 255)          | 30 (18 - 250)                     | 33 (19 - 255)                   | 0.21  \\
| Prothrombin time, s                  | 17 (9 - 163)           | 16 (9 - 151)                      | 19 (11 - 163)                   | 0.26  \\
| Thrombin time, s                     | 21 (17 - 190)          | 24 (19 - 190)                     | 20 (17 - 179)                   | 0.29  \\
| Fibrinogen concentration, mg/dL      | 190 (22 - 825)         | 175 (22 - 789)                    | 198 (35 - 825)                  | 0.47  \\
| D-dimer concentration, ng/mL         | 167 (2 - 81,000)       | 172 (4 - 81,000)                  | 161 (2 - 69,000)                | 0.35  \\
| Promyelocytes in BM, %               | 71 (30 - 100)          | 72 (4 - 100)                      | 68 (30 - 90)                    | 0.40  \\
| Risk category, n (%)                 |                       |                                   |                                 | 0.042 \\
| Low                                  | 136 (37.8)             | 86 (42.0)                         | 50 (32.3)                       |       \\
| Intermediate                         | 81 (22.5)              | 49 (23.9)                         | 32 (20.6)                       |       \\
| High                                 | 143 (39.7)             | 70 (34.1)                         | 73 (47.1)                       |       \\

BM: bone marrow; CNS: central nervous system; COPD: chronic obstructive pulmonary disease; DIC: disseminated intravascular coagulation; NA: not available.

Table 2. ATRA Treatment and Response to Induction Therapy

| Characteristic                          | All patients (N = 360) | Daunorubicin recipients (n = 205) | Idarubicin recipients (n = 155) | \( P \)  \\
|----------------------------------------|------------------------|-----------------------------------|---------------------------------|---------  \\
| Treated with ATRA, n (%)               | 339 (94.2)             | 201 (98.0)                        | 138 (89.0)                      | 0.001  \\
| Initiated at diagnosis                 | 284 (83.8)             | 184 (91.5)                        | 100 (72.5)                      | 0.0001  \\
| Initiated > 1 day after diagnosis      | 55 (16.2)              | 17 (8.5)                          | 38 (27.5)                       | 0.02  \\
| Median time to start of ATRA, days (range) | 4 (1 - 27)            | 2 (1 - 18)                        | 5 (3 - 27)                      | 0.32  \\
| Median duration of ATRA treatment, days (range) | 75 (45 - 95)        | 73 (45 - 89)                      | 77 (52 - 95)                    | 0.41  \\
| Response to induction therapy, n (%)   |                       |                                   |                                 | 0.04  \\
| CR                                     | 310 (86.1)             | 187 (91.2)                        | 123 (79.4)                      |       \\

ATRA: all-trans retinoic acid; CR: complete response.
was achieved in 1973, when it was shown that high CR rates could be achieved with daunorubicin monotherapy [21]. Nevertheless, the prognosis for patients with APL remained poor until the introduction of ATRA in the 1980s [5, 22, 23] and ATO in the following decade [5, 24, 25]. Numerous studies have since demonstrated the beneficial effects of adding ATO to ATRA, either with or without chemotherapy [26-35], leading to the approval of this combination in Europe [14] and the US [13] for the treatment of newly diagnosed, low-to-intermediate risk APL. ATO is not currently available in Mexico; however, hence the preferred treatment for APL in this country is anthracycline and ATRA-based induction and consolidation, followed by ATRA-based maintenance. Using this treatment approach, patients in our study achieved OS and EFS rates of

![Figure 1. Overall survival. (a) All patients. (b) By anthracycline.](image-url)
84% and 79%, respectively, after a median follow-up of 150 months post-diagnosis. These survival rates are generally similar to those reported in previously published clinical trials of anthracycline plus ATRA-based induction and consolidation followed by at least 1 year of maintenance therapy (Table 5) [31, 33, 34, 36-40], although follow-up times in the majority of those trials were substantially shorter than the 150-month median follow-up in our study.

Adding ATO to ATRA induction has been shown to improve outcomes versus an anthracycline plus ATRA. Patients included in the phase 3 APL0406 trial were randomized to either ATRA plus ATO as induction and consolidation therapy, or idarubicin plus ATRA-based induction and consolidation followed by ATRA-based maintenance for 2 years [33]. After a median follow-up of 40.6 months, 50-month OS was estimated at 99% in the ATO arm vs. 93% in the idarubicin arm (P = 0.0073), and 50-month EFS at 97% vs. 80% (P < 0.001), respectively [34]. In the AML17 trial, in which patients received induction and consolidation treatment based on ATRA plus either idarubicin or ATO, 4-year EFS was significantly prolonged in the ATO arm vs. the idarubicin arm (91% vs. 70%, P = 0.002) [41]. In the light of such findings, it seems reasonable

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**Figure 2.** Event-free survival. (a) All patients. (b) By anthracycline.
Treatment with ATRA should be initiated as soon as APL is suspected, even before the diagnosis is confirmed [6]. However, if the diagnosis is not corroborated either genetically or molecularly, ATRA should be discontinued [6]. In patients with WBC ≤ 10 × 10^9/L, administration of ATO or chemotherapy may be delayed until the diagnosis of APL is confirmed; in those with WBC > 10 × 10^9/L, chemotherapy should be initiated without delay [6]. Wherever possible, bone marrow samples should be used to confirm the genetic diagnosis of APL [6]. Although the PML/RARA fusion gene can be identified using any of a variety of techniques, including conventional karyotyping or fluorescence in situ hybridization (FISH), only

Table 3. Uni- and Multivariate Analysis of Factors Influencing Overall Survival (N = 360)

| Variables | Univariate HR (95% CI) | P | Multivariate HR (95% CI) | P |
|-----------|------------------------|---|--------------------------|---|
| Age (<35 years vs. ≥ 35 years) | 1.02 (1.00 - 1.04) | 0.016 | 1.01 (0.96 - 1.36) | 0.01 |
| Risk category (low vs. intermediate vs. high) | 2.20 (1.56 - 3.27) | 0.001 | 1.92 (1.32 - 2.79) | 0.01 |
| Anthracycline type (daunorubicin vs. idarubicin) | 1.55 (1.18 - 2.04) | 0.001 | 1.17 (0.87 - 1.58) | 0.02 |
| DS (yes vs. no) | 1.81 (0.77 - 4.23) | 0.160 | 1.10 (0.46 - 2.65) | 0.82 |
| ATRA treatment (yes vs. no) | 1.00 (0.57 - 1.76) | 0.002 | 0.45 (0.33 - 0.89) | 0.01 |
| Timing of ATRA initiation (day 0 vs. after day 1) | 1.40 (0.81 - 2.44) | 0.020 | 0.76 (0.55 - 1.10) | 0.04 |
| DIC (yes vs. no) | 0.99 (0.73 - 1.00) | 0.030 | 0.81 (0.66 - 1.12) | 0.02 |

ATRA: all-trans retinoic acid; CI: confidence interval; DIC: disseminated intravascular coagulation; DS: differentiation syndrome; HR: hazard ratio.

Table 4. Reported Complications and Antibiotic Treatment Received

| Treatment | All patients (N = 360) | Daunorubicin recipients (n = 205) | Idarubicin recipients (n = 155) | P |
|-----------|------------------------|--------------------------|--------------------------|---|
| DS | 66 (18.3) | 33 (16.1) | 33 (21.3) | 0.22 |
| FN | 336 (93.3) | 193 (94.1) | 143 (92.3) | 0.44 |
| Antibiotic treatment for FN | | | | 0.098 |
| Ceftazadime/amikacin | 160 (44.4) | 88 (42.9) | 72 (46.5) | |
| Imipenem | 124 (34.4) | 61 (29.8) | 63 (40.6) | |
| Levofloxacin | 52 (14.4) | 44 (21.5) | 8 (5.2) | |

Values are expressed as n (%). DS: differentiation syndrome; FN: febrile neutropenia.

Table 5. Survival Rates in Published Clinical Trials of Anthracycline Plus ATRA-Based Induction and Consolidation Treatment for APL

| Trials | Treatment regimen | Number of patients | OS | EFS |
|--------|------------------|--------------------|----|-----|
| AIDA 0493 [36] | Idarubicin and ATRA-based induction and consolidation; maintenance for 2 years | 828 | 77% at 12 years | 69% at 12 years |
| APL0406 [33, 34] | Idarubicin and ATRA-based induction and consolidation; maintenance for 2 years | 137 | 93% at 50 months | 80% at 50 months |
| IC-APL 2006 [38] | Daunorubicin and ATRA-based induction and consolidation; maintenance for 2 years | 183 | 80% at 2 years | 77% at 2 years |
| PETHEMA LPA 99 [39] | Idarubicin and ATRA-based induction and consolidation; maintenance for 2 years | 560 | 82% at 5 years | NR |
| PETHEMA LPA 2005 [40] | Idarubicin and ATRA-based induction and consolidation; maintenance for 2 years | 404 | 88% at 4 years | NR |
| MR AML15 [37] | Idarubicin and ATRA-based induction and consolidation; maintenance for 2 years | 146 | 84% at 5 years | NR |
| North American Leukemia Intergroup Study C9710 [31] | Daunorubicin and ATRA-based induction and consolidation; maintenance for 1 year | 237 | 81% at 3 years | 63% at 3 years |

APL: acute promyelocytic leukemia; ATRA: all-trans retinoic acid; EFS: event-free survival; NR: not reported; OS: overall survival.
RT-PCR or real-time quantitative (RQ-) PCR will enable definition of the type of PML-RARA isoform and its quantification for subsequent MRD measurement [6, 42].

In a study of 217 patients with newly diagnosed PML/RARA-positive APL who received ATRA plus chemotherapy as maintenance following induction and consolidation treatment, multivariate regression analysis identified initial WBC and platelet counts as the only variables that were independently prognostic for relapse-free survival (RFS) [43]. On the basis of these findings, the authors developed a predictive model that defined three risk groups, as follows: low risk - WBC \(\leq 10 \times 10^9/L\) and platelet count \(\leq 40 \times 10^9/L\); intermediate risk - WBC \(\leq 10 \times 10^9/L\) and platelet count \(\leq 40 \times 10^9/L\); and high risk - WBC > \(10 \times 10^9/L\). In the approach taken by the NCCN, risk stratification is based solely on WBC counts, and platelet counts as the only variables that were independently prognostic for RFS [43].

The 91% CR rate that we observed following induction with ATRA and chemotherapy in APL patients in IC-APL 2006, Mexican patients accounted for only 16% of the patient population, with the remainder coming from South American nations. It is possible, therefore, that not only ethnicity, but also geographical factors contribute to the risk profile of patients with APL. Ethnicity has previously been found to be associated with the incidence of APL and the survival of patients with APL. In separate studies, Duerer et al [44] and Estey et al [45] reported an increased incidence of APL among Latinos versus non-Latinos with AML. Although Matasar et al found no significant difference in the lifetime incidence of APL in Hispanic versus non-Hispanic white populations, they did observe significantly higher APL incidence rates in Hispanic versus non-Hispanic white children (age 1 - 19 years, \(P = 0.02\)) and adults aged 20 - 44 years (\(P = 0.004\)) [46]. A retrospective Surveillance, Epidemiology, and End Results (SEER) database analysis that included 2,962 patients diagnosed with APL from 2000 through 2014 found that, compared with other ethnic groups, Hispanic ethnicity was associated with significant increases in both APL incidence per 100,000 population and early mortality rates [47]. Additionally, in a retrospective study of patients residing at the border between the USA and Mexico, age-adjusted OS was significantly worse among Hispanic patients with APL vs. non-Hispanic white patients [48].

In our study, high-risk patients accounted for 34% of daunorubicin recipients and 47% of those treated with idarubicin. The 91% CR rate that we observed following induction with daunorubicin plus ATRA is similar to the 90% and 85% CR rates reported among patients who received daunorubicin and ATRA-based induction in North American Leukemia Intergroup Study C9710 [31] and the IC-APL 2006 trial [38], respectively. Twenty-three percent of the C9710 population were high risk, compared with 32% of the IC-APL 2006 population, as already noted. Following daunorubicin and ATRA-based consolidation and ATRA-based maintenance therapy, patients randomized to the standard-therapy arm of C9710 achieved 3-year OS and EFS rates of 81% and 63%, respectively [31], while 2-year OS and EFS rates in IC-APL 2006 were 80% and 77%, respectively [38]. Although not obtained in head-to-head trials, the 150-month OS and EFS rates of 84% and 79% in the daunorubicin group in our study appear quite favorable by comparison with these outcomes. Rates of CR, 50-month OS and 50-month EFS in the 137 low-to-intermediate risk patients randomized to the idarubicin arm in the APL0406 trial were 97%, 93% and 80%, respectively [33, 34]. The AIDA 0493 study, in which 28% of the 807 patients were categorized as high risk, reported a 94% CR rate following induction with idarubicin plus ATRA [36]. While that figure is higher than the 79% CR rate in the idarubicin group in our study, EFS rates in the two studies were similar following three intensive consolidation cycles and maintenance treatment: 72% at 12.5 years among idarubicin recipients in our study vs. 69% at 12 years in AIDA 0493 [36]. Taken together, these results demonstrate that, in the absence of ATO, ATRA and anthracycline-based induction followed by intensive consolidation and maintenance therapy is a highly effective treatment strategy for patients with APL of any risk category.

We observed a higher CR rate among patients who received daunorubicin- vs. idarubicin-based induction and consolidation therapy. Furthermore, both OS and EFS rates at 150 months were significantly prolonged in the daunorubicin group vs. the idarubicin group. DS and FN were reported in similar percentages of patients in the two groups, however, indicating no difference in toxicity profiles. It should be noted that the two patient groups in our study differed in a few important aspects. A significantly higher proportion of patients in the idarubicin group vs. the daunorubicin group had DIC at diagnosis, while a higher percentage of daunorubicin recipients received ATRA induction, started ATRA treatment on day 1, and achieved a CR following induction treatment. Each of these factors could have contributed to the improved outcomes observed in the daunorubicin group vs. the idarubicin group, therefore no firm conclusions regarding the relative efficacy of daunorubicin- vs. idarubicin-based induction and consolidation can be drawn from our data. Prospective, randomized, comparative studies are required to clarify whether differences do, indeed, exist in the efficacy of these two anthracyclines when combined with ATRA in the treatment of APL.

As this was a retrospective chart review, and access to diagnostic tests and tools at the participating institutions was limited, the results reported in this paper must be interpreted with caution. Nevertheless, they provide valuable information about the incidence of APL in Mexico, the characteristics of Mexican patients at diagnosis and the efficacy of treatment strategies currently followed in this country.

**Conclusions**

Guidelines published by the NCCN identify ATRA plus ATO as the preferred treatment option for patients with APL of all risk categories. Where ATO is either unavailable or contrain-
dicated, anthracycline-based treatment is recommended as an alternative. The findings of the present study demonstrate that, in newly diagnosed Mexican patients with APL, treatment with either daunorubicin or idarubicin plus ATRA results in high CR rates following induction, and long-term OS and EFS rates of around 80% after intensive consolidation and maintenance. These results are in line with those of previously published clinical trial data, and confirm the benefits of treatment with anthracycline plus ATRA-based regimens in patients with APL of any risk category when ATO is contraindicated or otherwise unavailable.

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Financial Disclosure

None to declare.

Conflict of Interest

The authors have no potential conflict of interest to disclose.

Informed Consent

Written informed consent was obtained from all study participants.

Author Contributions

NZ-C and MA designed the study. LA produced the first draft of the manuscript. MA-I analyzed the data. All the authors collected patient data, and read and approved the final manuscript.

Data Availability

The data analyzed during the study are available from the corresponding author on reasonable request.

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