Original Study

Is There Still a Role for Low-Dose All-Transretinoic Acid in the Treatment of Acute Promyelocytic Leukemia in the Arsenic Trioxide Era?

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Abstract

According to pharmacokinetic studies, low and standard doses of all-transretinoic acid (ATRA) have shown similar plasma concentrations. Based on this, as well as on the financial constraints of our uninsured patients, we evaluated the efficacy of low-dose ATRA (LD-ATRA) plus anthracycline-based chemotherapy in 22 newly diagnosed patients with acute promyelocytic leukemia (APL) and concluded that it is safe and effective in achieving complete remission (CR); however, the relapse rate was 27.2%, which is higher than the expected relapse rate using standard doses of ATRA.

Background: Low-dose all-transretinoic acid (LD-ATRA) has shown similar peak plasma concentrations and a mean area under the concentration time curve in comparison with standard doses of ATRA. We evaluated the efficacy of LD-ATRA plus anthracycline-based chemotherapy in patients with newly diagnosed acute promyelocytic leukemia (APL). **Patients and Methods:** Patients diagnosed with APL during the period of 2002 to 2014 were included. They received ATRA 25 mg/m^2 plus anthracycline (doxorubicin or mitoxantrone) as induction chemotherapy, followed by 3 consolidations with LD-ATRA and anthracycline and maintenance therapy with intermittent LD-ATRA and oral chemotherapy for 2 years. **Results:** Twenty-two patients with a median age of 28 years (range, 18-55 years) were included; 17 (77%) were in the low-risk group. Complete remission occurred in 86%, and the early death rate was 9%. At a median follow-up of 32 months (range, 4-126 months) disease-free survival (DFS) was 75% and overall survival (OS) was 86%, with a relapse rate of 27% for the entire follow-up period. **Conclusion:** LD-ATRA plus anthracycline is safe and effective in achieving CR of APL. The early death rate is similar to that of treatment with standard doses, but it appears to be inferior in preventing relapses.

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Introduction

Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia, classified as AML M3 in the French-American-British classification system. It is characterized by a reciprocal chromosomal translocation (15;17) (q22;q12), resulting in fusion between the promyelocytic gene on chromosome 15 and the retinoic acid receptor-α of chromosome 17 (RARα), with this leading to the formation of an oncoprotein, PML-RARα.[1] The percentage of AML that corresponds to APL varies from 5% to 8%, with APL being more common among Hispanics than non-Hispanics.[1-3]

In 1985, all-transretinoic acid (ATRA) was introduced for the treatment of APL. Its combination with anthracyclines yielded complete remission rates of 90% to 95% and disease-free survival (DFS) of up to 85% for low-risk patients who survived remission induction. Even better outcomes were achieved after arsenic trioxide (ATO) was introduced in the mid-1990s, reaching a 5-year relapse-free survival (RFS) of 94%.[4,5] Early death resulting from hemorrhage remains a major cause of induction failure, reaching 10% in recent studies.[6]

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The standard treatment scheme for APL includes ATRA 45 mg/m^2 per day until complete remission is achieved, along with anthracycline.[7] However, cost is a major concern in developing countries. In Mexico, the minimum daily wage is around $5 USD per day,[8] whereas each 10-mg capsule of ATRA costs approximately $10 USD, making it unaffordable for individuals without health care coverage (about 50% of the Mexican population).[9] ATO is considerably more expensive and is not commercially available in Mexico.[1]

In 1993, a pharmacokinetic study showed that the peak plasma concentrations and the mean area under the concentration time curve for an ATRA dose of 25 mg/m^2 were similar to the levels obtained with a dose of 45 mg/m^2, with no therapeutic difference.[10] Later in 1996, another pharmacokinetics study compared 15 mg/m^2 and 45 mg/m^2 doses. The results showed that differentiation was achieved equally with both doses, and the maximal plasma concentration obtained with this dose was sufficiently high, achieving complete response in 92% of de novo cases of APL treated with 15 to 20 mg/m^2.[11] Therefore, in this study we report the results of administering a reduced dose of ATRA of 25 mg/m^2 to patients with APL over a 12-year period. This dose was based on the previous information and the financial constraints of our low-income uninsured patients who must pay for their treatment.

Patients and Methods

All patients diagnosed with APL who received treatment from the onset of disease at the "Dr José Eleuterio González" University Hospital of the Universidad Autónoma de Nuevo León from January 1, 2002 to July 31, 2014 were included in the study. The diagnosis of APL was made morphologically and was confirmed with the demonstration of PML/RARα fusion transcripts by polymerase chain reaction or of t(15;17) by fluorescence in situ hybridization.[5,12] Patients were classified by risk category, with low-risk patients considered to be those with a white blood cell count of $< 10{,}000/\mu L$ and high-risk patients being those with a leukocyte count $> 10{,}000/\mu L$.[13]

Treatment Protocol

For induction therapy, the original treatment protocol with ATRA + idarubicin (AIDA)[14] was modified as follows: LD-ATRA (25 mg/m^2/d) until complete remission (CR) and doxorubicin 45 mg/m^2/d or mitoxantrone 10 mg/m^2/d for 3 consecutive days starting on day 3 until day 5. Patients with evidence of APL differentiation syndrome were treated with dexamethasone.[15]

After evidence of hematologic recovery was observed, all patients received consolidation therapy consisting of 3 cycles of doxorubicin (45 mg/m^2/d) or mitoxantrone (10 mg/m^2/d) on days 1 to 3, in combination with LD-ATRA for 15 days. At the end of consolidation therapy, molecular remission was evaluated by fluorescence in situ hybridization or polymerase chain reaction. 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/wk on days 1 to 60 and ATRA 25 mg/m^2/d on days 61 to 75.

Evaluation of Response

The criteria of the International Working Group were used to define hematologic and molecular CR and relapse.[16] Early death was defined as death occurring during induction therapy. Overall survival (OS) was defined as the time from diagnosis to death from any cause or the end of follow-up. DFS was defined as the time from CR to relapse, death, or the end of follow-up.

Table 1 Clinical Features of Patients With APL

Characteristics (n = 22)	Median (Range), n (%)
Age (years)	28 (18-55)
Sex	
Male	10 (45.5%)
Female	12 (54.5%)
Risk group	
High	5 (22%)
Low	17 (77.3%)
WBC count ($\times 10^3/\mu L$) median (range)	2.3 (0.08-46.9)
Platelet count ($\times 10^3/\mu L$) median (range)	15.6 (3-103)
Hb (g/dL) median (range)	7.1 (3.1-12.3)

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

Statistical Analysis

OS and DFS were assessed using the Kaplan-Meier method. Univariate and multivariate analysis was performed using the Cox regression model for all risk factors described. Differences among groups for qualitative variables were analyzed with Fisher's exact test or the χ^2 test. A P value less than .05 was considered statistically significant, and all tests were 2-sided.

Results

Twenty-two patients were diagnosed with APL during the study period. Patient characteristics are shown on Table 1. Median age at diagnosis was 28 years, with a range of 18 to 55 years; 45.5% of patients were men. Most patients were in the low-risk group (77.3%). Two patients died because of intracranial hemorrhage on days 2 and 3, respectively, with an early death rate of 9.1%. The CR rate after induction was 86.3% (19 of 22 patients).

The median follow-up period was 32 months, with the longest being 126 months. At 32 months, OS was 86% and DFS was 75% for the whole group, whereas OS was 60% and 94% in the high- and low-risk groups, respectively, with the difference being statistically significant ($P = .03$) (Figure 1).

Treatment and Outcome of Relapse Patients

Six patients (27.2%) had relapsed disease (2 women and 4 men). The median age of this group was 23 years. Two patients belonged to the high-risk group. These patients experienced disease relapse at a mean of 32 months (range, 20-55 months). Five had bone marrow involvement and 1 had isolated central nervous system relapse. At the time of this report, 3 of these patients were receiving induction treatment for relapse with LD-ATRA and mitoxantrone 10 mg/m^2/d for 3 days. The patient who experienced central nervous system relapse received treatment with LD-ATRA, high-dose arabinofuranosyl cytidine (ara-C), intrathecal chemotherapy followed by ATO, and autologous stem cell transplantation, achieving CR. This patient is alive and in CR 8 years later.