

Effect of all-trans retinoic acid on newly diagnosed acute promyelocytic leukemia patients: results of a Brazilian center

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Abstract

Thirty-seven patients with acute promyelocytic leukemia (APL) were treated with all-trans retinoic acid (ATRA). Patients received $45 \text{ mg m}^{-2} \text{ day}^{-1}$ *po* of ATRA until complete remission (CR) was achieved, defined as: a) presence of less than 5% blasts in the bone marrow, with b) white blood cells $>10^3/\text{mm}^3$, c) platelets $>10^5/\text{mm}^3$ and d) hemoglobin concentration $>8 \text{ g/dl}$, with no blood or platelet transfusions. Thirty-one (83.7%) patients achieved CR by day 50, and 75% of these before day 30. Correction of the coagulopathy, achieved between days 2 and 10 (mean, 3 days), was the first evidence of response to treatment. Only one patient had been previously treated with chemotherapy and three had the microgranular variant M3 form. Dryness of skin and mucosae was the most common side effect observed in 82% of the patients. Thrombosis, hepatotoxicity and retinoid acid syndrome (RAS) were observed in 7 (19%), 6 (16%) and 4 (11%) patients, respectively. Thirteen (35%) patients had to be submitted to chemotherapy due to hyperleukocytosis (above $40 \times 10^3/\text{mm}^3$) and six of these presented with new signs of coagulopathy after chemotherapy. Four (11%) patients died secondarily to intracerebral hemorrhage (IH) and two (5.4%) dropped out of the protocol due to severe ATRA side effects (one RAS and one hepatotoxicity). RAS and IH were related strictly to hyperleukocytosis. The reduced use of platelets and fresh frozen plasma probably lowered the total cost of treatment. We conclude that ATRA is an effective agent for inducing complete remission in APL patients.

Key words

- All-trans retinoic acid
- Acute promyelocytic leukemia
- Retinoid acid syndrome

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Introduction

Acute promyelocytic leukemia (APL), or M3 in the French-American-British classification, represents 5-15% of cases of acute myeloid leukemia (AML) (1). This distinct subset of AML is associated with the presence of abnormal promyelocytes in the blood

and bone marrow, associated with a consumptive coagulopathy combining disseminated intravascular coagulation (DIC), fibrinolysis and proteolysis (2). Furthermore, a specific chromosomal abnormality (1), represented by a balanced reciprocal translocation between chromosomes 15 and 17, results in the union of portions of the promy-

elocytic leukemia gene with the gene for retinoic acid receptor alpha (3). As demonstrated initially by Huang et al. (4), patients with APL have a high response rate to differentiation therapy with all-trans retinoic acid (ATRA), even though complete remission (CR) has not been sustained by ATRA therapy alone (5). One major advantage of the ATRA schedule is that it results in rapid disappearance of DIC (4), mainly through cytodifferentiation rather than immediate lysis of leukemic cells. However, some new life-threatening retinoid-induced complications, such as leukocytosis, retinoid acid syndrome (RAS) and thromboembolic events, have been demonstrated in a significant number of cases (6). In spite of several studies reporting the efficacy of the differentiating therapy with ATRA, no reports have been published thus far in the Brazilian literature. The authors present 37 patients with APL from two major cancer centers from Curitiba, Brazil, where induction therapy, toxicity and treatment costs of ATRA were assessed.

Patients and Methods

Patients and eligibility criteria

Between March 1992 and November 1995, 37 patients (Table 1) diagnosed with APL from Hospital de Clínicas and Hospital Nossa Senhora das Graças, Curitiba, were included in a clinical trial to evaluate the efficacy of ATRA in inducing CR and its toxicity. Patients or their legal representatives gave informed consent to participate in the experimental study, which was approved by the Ethics Commissions of both hospitals. Inclusion criterion was a diagnosis of APL based on FAB group morphology criteria (7). Although cytogenetic evaluation for t(15;17) was attempted for most patients, demonstration of the PML-RAR α protein was not required as a criterion for eligibility. Prior to the beginning of ATRA therapy, complete coagulation studies and normal

hepatic and renal function tests were required.

Protocol design

Patients received 45 mg m⁻² day⁻¹ *po* of ATRA (Tretinoína, Roche Pharmaceuticals, São Paulo, Brazil) until day 50 of ATRA or refractoriness was demonstrated. When the coagulopathy was still present beyond the 10th day of treatment, ATRA was increased to 90 mg m⁻² day⁻¹ *po* for 5 additional days. If no correction of DIC occurred, aggressive chemotherapy was started. CR was defined on days +30 or +50 of ATRA therapy on the basis of peripheral blood counts and bone marrow aspiration and biopsy studies as: 1) presence of less than 5% blasts in the bone marrow, with 2) white blood cells >10³/mm³, 3) platelets >10⁵/mm³ and 4) hemoglobin concentration >8 g/dl, with no blood or platelet transfusions. Red blood cell transfusion was used to maintain hemoglobin levels above 8 g/dl and platelet transfusion was performed to maintain platelet count above 20 x 10³/mm³. Fresh frozen plasma and cryoprecipitate transfusions were performed in patients with any evidence of coagulopathy (6). Patients with severe thrombotic phenomena such as pulmonary embolism and large vein thrombosis received heparin 5000 U *iv* q4h for 10 days, followed by heparin 5000 U *sc* bid until the end of the ATRA therapy. Those who reached white blood cell count (WBC) above 40 x 10³/mm³ were managed with cytosine arabinoside (500 mg/m², *iv*) and daunomycin (60 mg/m², *iv*) in order to decrease tumor mass. RAS, characterized by unexplained fever, weight gain, respiratory distress, interstitial pulmonary infiltrates, pleural and pericardial effusions, and generally accompanied by leukocytosis (8), was managed with dexamethasone 10 mg *iv* bid for at least 3 days. Antibiotics were given as supportive treatment when necessary (findings of localized infection or fever of unknown origin in patients with granulocyte counts below 500/mm³).

Laboratory follow-up

Daily complete blood cell counts (CBC) and coagulation studies were performed after initiating the ATRA therapy until stabilization of leucocytes and correction of coagulopathy, respectively. The studies were repeated once a week until day +30 or +50 of ATRA therapy. A bone marrow aspirate was obtained on days +30 and +50 to check for CR. Hepatic and renal function tests were performed weekly during hospitalization and twice a month thereafter.

Endpoints

The major endpoints of this study were: 1) intolerance to ATRA, 2) maintenance of the coagulopathy beyond day 15 of ATRA therapy, 3) no CR after day 50, and 4) resistance to ATRA.

Results

Response to therapy

CR was achieved in 31 (83.7%) patients, by day 30 of ATRA treatment in 23 of them and by day 50 in 8, and no patient had the drug discontinued because of resistant disease. Correction of the coagulopathy was the first evidence of response to ATRA and was detected in 34 patients between days 2 and 10 (mean, 3 days). Thirteen patients had to be submitted to chemotherapy due to elevated WBC (above $40 \times 10^3/\text{mm}^3$) and six of these presented with new signs of coagulopathy after chemotherapy. Four (10.8%) patients died secondarily to central nervous system bleeding on days +4, +5, +7 and +18. Two had early death while on ATRA therapy only and two died after chemotherapy due to elevated WBC, and all four had leucocytes above $40 \times 10^3/\text{mm}^3$ at the time of death. Two patients dropped out of the protocol due to severe ATRA side effects (RAS in one and hepatotoxicity in the other). Median

WBC was $2.4 \times 10^3/\text{mm}^3$ (range 0.6 to $52 \times 10^3/\text{mm}^3$) for all patients at diagnosis, reaching a maximum of $24.3 \times 10^3/\text{mm}^3$ (range 4.2 to $100.6 \times 10^3/\text{mm}^3$) in all patients alive between days +6 and +19 (mean, +15 days) after initiating ATRA treatment.

Toxicity

The most common side effect of ATRA therapy was dryness of skin and mucosae in 82% (28) of the patients, which developed from the first to the third week. Severe thrombosis was observed in 7 (19%) patients, but only one had a WBC above $20 \times 10^3/\text{mm}^3$. RAS was diagnosed in 4 (11%) patients on days +3, +5, +10 and +15 of ATRA treatment. One of these patients received chemotherapy ordered by the attending physician instead of the proposed RAS treatment, and was excluded from the protocol. These patients presented a maximum median WBC of $48 \times 10^3/\text{mm}^3$, compared to $22.5 \times 10^3/\text{mm}^3$ ($P < 0.05$, Fisher's test (9)) in patients with no RAS. Six patients presented increased values of liver function tests, but only one had

Table 1 - Characterization of the patient population.

Characteristics	
Number of patients	37
Age, years (range)	17.5 (9-69)
Sex (M/F)	17/20
Morphology	
Classical M3	34
Microgranular variant M3	3
Clinical status	
Fever	10 (27%)
Bleeding	10 (27%)
Ecchymosis	34 (92%)
Laboratory data (range)	
WBC/mm ³	
Classical M3	3000 (600-51200)
Microgranular variant M3	26200 (5600-52000)
Hemoglobin (g/dl)	8.0 (4.0-12.3)
Platelets/mm ³	21000 (9000-162000)
Peripheral blood blasts (%)	56 (0-94)
Fibrinogen (mg/dl)	189 (44-360)
PT (s)	17.1 (12-42)
PTT (s)	34.6 (17-65)

severe intrahepatic cholestasis with liver function tests reaching values 8 times higher than the normal upper limit and was withdrawn from the protocol.

Supportive care and hospitalization

Hospitalization varied from 0 to 50 days (mean, 19 days). The amount of blood components utilized during this time is summarized in Table 2. The amount of platelets and fresh frozen plasma transfused in the ATRA group was significantly less than for the chemotherapy group, 31.7 IU versus 135 IU ($P = 0.05$) and 100 ml versus 1,330 ml ($P < 0.01$), respectively. Thirteen patients had to be managed with antibiotics (one due to periodontitis, one due to tonsillitis, another due to scrotal sac cellulitis and the rest due to fever of unknown origin during the leukopenic period).

Discussion

APL is a distinct subgroup of AML with specific clinical and molecular features. Over the last few years, the introduction of ATRA has opened new perspectives for the treatment and understanding of several of its leukemic mechanisms. This study shows the differentiating capacity of ATRA as an inductor of CR, with 83.7% of the newly diagnosed patients achieving CR during the course of treatment. Such remission rates are similar to those obtained in several other randomized trials with ATRA (4,10) and also to the historical results obtained with

standard chemotherapy (11).

DIC is the most common complication of APL and its severity and frequency are often aggravated by chemotherapy, as was the case for 6 of our patients. Although patients submitted to chemotherapy frequently reach CR, they usually need intensive blood support to prevent bleeding, attributed to the release of both procoagulatory and fibrinolytic substances from damaged malignant cells, low fibrinogen levels and worsening of thrombocytopenia. In our own service, we compared historical data of 28 patients treated with chemotherapy alone from 1985 to 1992 with those for the group treated with ATRA. The first evidence of a response to ATRA in our patients was correction of the coagulopathy (mean, 3 days), with a rapid resolution of fibrinolysis and fibrinogenopenia, consequently reducing the amount of blood components needed and the possible implications of hemorrhagic diathesis, as reported by several other authors (9,12,13).

Leukocytosis, an adverse effect of ATRA therapy in APL (14), which occurred in 37% of our patients, is due to an increase in circulating maturing blast cells secondary to cytodifferentiation rather than leukemic cell lysis, and is not observed during conventional intensive chemotherapy. The high number of circulating blasts increases blood viscosity and is associated with leukoblastic emboli, resulting in leukostasis of the small vessels. Furthermore, the leukemic blasts can infiltrate the arteriolar endothelial walls and cause a secondary hemorrhage (15). Therefore, a major concern about APL patients treated with ATRA is early death secondary to hyperleukocytosis during induction treatment (11,16), especially due to RAS and intracerebral hemorrhage. In our study, 4 of 37 patients (11%) had an early death due to intracerebral hemorrhage, with a higher median WBC than in the group that did not develop this lethal complication ($48 \times 10^3/\text{mm}^3$ versus $22.5 \times 10^3/\text{mm}^3$). RAS also occurred only in patients whose leuko-

Table 2 - Utilization of blood components in ATRA patients.

Blood component	Median amount of blood components (IU/patient)
Platelets	37.2
Red blood cells	3.6
Fresh frozen plasma	12.5
Fresh plasma	180 ml

cytes were above $40 \times 10^3/\text{mm}^3$ (4 of 13 patients).

In order to avoid hyperleukocytosis and its complications, the French group designed a protocol whose major goal was to prevent the increase in leukocyte counts by the early use of chemotherapy in combination with ATRA (17,18), but this strategy barely improved their CR rates. Vahdat et al. (19), analyzing the concept of full-dose chemotherapy based on the peripheral blood leukocyte count proposed by the French group, demonstrated that chemotherapy actually contributes to excess early mortality due to the reappearance of the bleeding diathesis, a fact that was also observed in the present study. Indicating how hard it is to establish an ideal leukocyte parameter for the combination of early chemotherapy with ATRA, several Chinese reports have found a very low incidence of RAS despite very high leukocyte counts (4,5,20). In agreement with Fenau et al. (21), we may speculate about the presence of genetic predisposition to RAS among different populations, explaining these intriguing differences.

In our group, 3 of the 4 patients with RAS were managed with a short course of high-dose dexamethasone and had their abnormalities corrected, just as demonstrated by others (8,22). Based on these results, the serious complications of RAS have been almost entirely eliminated with a liberal policy of steroid administration, substantially reducing mortality. We note, however, that this approach mandates careful patient monitoring, particularly with respect to fluid balance and renal function. As a step ahead in the management of these patients, how would one avoid the occurrence of RAS? Strategies such as prophylactic corticosteroids (22,23), concomitant use of ATRA and hydroxyurea (22) and lower doses of ATRA (20) (15 to 25 mg/m²) have been applied with acceptable results, but not yet evaluated in randomized trials.

As in other subtypes of acute leukemias,

APL patients show a strict relationship between leukocytosis and severe hemorrhage. In our group, 4 patients died of intracerebral hemorrhage and all had leukocyte counts above $40 \times 10^3/\text{mm}^3$ at the time of bleeding, versus a $22 \times 10^3/\text{mm}^3$ leukocyte count in patients who did not present this complication. Since all our patients were submitted to the same approach in terms of platelet transfusion and the coagulation abnormalities had been corrected at time of death, we conclude that hyperleukocytosis is probably involved in the etiology of retinoid-induced intracerebral hemorrhage.

ATRA therapy rapidly corrects the bleeding diathesis and normalizes the fibrinogen levels of APL patients. However, a procoagulant tendency persists due to the existence of low grade DIC which accounts for the thrombotic events seen as late as 1 month after ATRA therapy (24) and for the 10% hemostatic death rate reported among these patients (25). Furthermore, patients treated with conventional chemotherapy alone rarely develop thromboembolic events (2). Seven patients in whom we clinically detected these phenomena during ATRA therapy were successfully managed with heparin. In spite of some reports implicating thromboembolism in leukocytosis (26,27), no relationship was noticed between these complications in our patients, and only one had leukocytes above $20 \times 10^3/\text{mm}^3$ at the time of thrombosis. Some authors even recommend the prophylactic administration of low molecular weight heparin for one month in order to avoid thrombotic events in these patients (24).

ATRA given during induction did not improve the rate of CR or decrease mortality (28), but these patients developed less frequent and severe hemorrhagic complications, demanding a decreased amount of platelets and fresh frozen plasma, probably reducing the cost of care and the chance of transmission of blood-borne diseases when compared to patients managed with standard chemotherapy. The side effects of ATRA may

be considered predictable, so that avoiding leukocytosis above $20 \times 10^3/\text{mm}^3$ would significantly reduce the possibility of RAS and probably of intracerebral hemorrhage. Careful clinical monitoring of these patients would also allow an early diagnosis of thrombotic

complications. Based on these observations we conclude that ATRA is an effective agent for the induction of CR in APL patients, and therefore we recommend its use for induction therapy in all patients with APL.

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The application deadline is October 1, 1999. Winners will be notified in April 2000 and the fellowship should begin no later than August 2000.

Deadline for applications: October 1, 1999

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