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ORIGINAL ARTICLE

All-*trans* Retinoic Acid and Intensive Chemotherapy in Acute Promyelocytic Leukemia

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- **Abstract**

Background-All-*Trans* Retinoic Acid (ATRA) is a subgroup of the retinoid family, which induces a complete remission in acute promyelocytic leukemia (APL). It causes differentiation and apoptosis in immature malignant promyelocytes. It is not clear whether induction therapy with ATRA followed by intensive chemotherapy is superior to chemotherapy alone in the outcome of these patients.

Objective-To investigate the results of treatment with ATRA and intensive chemotherapy in acute promyelocytic leukemia (APL).

Methods-A total of thirty patients were enrolled into the study and were treated with ATRA in a prospective study at Shariati Hospital from 1996-99. ATRA was prescribed with a daily dose of 45 mg/m^2. In case of ATRA-induced maturation or hyperleukocytosis, intensive chemotherapy was given with cytarabine and idarubicin. This was followed by two additional courses of the same chemotherapy as consolidation. ATRA syndrome was treated with dexamethasone.

Results-At the time of diagnosis, clinical and subclinical coagulopathy and all-*trans*-retinoic acid induced maturation was seen in 96% and 73.3% of patients, respectively. In 26.7% of patients, the response was partial or inconspicuous. All clinical and laboratory evidence of coagulopathy was corrected during the ATRA therapy. ATRA syndrome occurred in 11(42.3%) patients. With a median follow-up period of 1.5 years, 65.4% of patients showed complete remission.

Conclusion-This study shows that ATRA is a safe and appropriate treatment for APL, which improves disease-free states and overall survival as compared with chemotherapy alone. We recommend the use of all-*trans* retinoic acid for induction therapy followed by intensive chemotherapy in patients with APL.

Keywords • All-*trans* retinoic acid • ATRA • acute promyelocytic leukemia • APL • intensive chemotherapy

Introduction

Acute promyelocytic leukemia (APL) is a specific subtype of acute myelogenous leukemia, which is identified by the following biological and clinical characteristics: 1) Over 50% of the bone marrow nucleated cells are malignant promyelocytes.[1,2] 2) A specific chromo-somal translocation, t (15; 17) is seen in nearly all cases of APL and has a basic role in retinoic acid receptor molecular distortion and maturation arrest of the myeloid series, thereby leading to an increase in the bone marrow malignant promyelocytes.[3,4] 3) Clinical and laboratory findings of disseminated intravascular coagulation (DIC) before or during treatment, which has a significant role in morbidity and mortality. This is due to the sudden release of a procoagulant factor and fibrinolysine from the immature promyelo-cytes following intensive chemotherapy.[5,6]

Standard chemotherapy with cytosine arabinoside and anthracycline yielded a complete remission rate of 50%-60%. Cure rate was seen in 25%-50% of APL patients after consolidation therapy.[7,8,9,10] Treatment failure was due to bleeding and uncontrollable infection as a result of severe prolonged pancytopenia. ATRA is a drug which causes gradual differentiation of the malignant promyelocytes, thereby reducing the incidence and severity of hemorrhage during

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treatment.[11,12] At present ATRA plus intensive chemotherapy is the standard therapeutic protocol. When compared to standard chemotherapy alone, it is seen to increase the complete remission rate, overall survival, and disease-free survival. In order to assess the effect of ATRA and intensive chemotherapy in APL, a pilot study was performed on 30 patients referred to the Hematology-Oncology Department of Shariati Hospital from other centers. In this study, intensive chemotherapy was administrated following complete morpho-logic remission with ATRA.

Methods

During the years 1996-99, the newly diagnosed APL patients entered a pilot study of treatment with ATRA followed by intensive chemotherapy. Diagnosis of APL was based on FAB classification and clinical and laboratory findings of DIC and documentation of specific translocation.[15,17]

Remission induction

ATRA 45 mg/m^2 was given in a single daily dose for a maximum of45 days . In case of development of retinoic acid syndrome, dexamethasone 10 mg (IV) was given twice a day for 3 to 5 days. Diagnosis of retinoic acid syndrome was made using the Frankel criteria. The main criteria are: Fever, tachypnea, weight gain, renal failure and hyperleukocytosis. If white blood cells increased to values over 20,000/mm^3, or if the promyelocytes increased more than 10,000/mm^3, dexamethasone was used along with ATRA and chemotherapy.

Consolidation

After complete morphologic maturation with ATRA or after 45 days, intensive chemotherapy was begun using cytosine arabinoside 300 mg/m^2, 24 hours continuous infusion for 5 days and idarubicin 12 mg/m^2, 30 minutes infusion for 3 days. The second and third consolidation cycles are the same as the first one and were started at an interval of 3-6 weeks depending on the patient's tolerance and hematological profile.

The major criteria for diagnosis of DIC were: 1) Fibrinogen less than 1 gr/liter. 2) Prolonged PT and PTT and 3) FDP more than 200 µgr/dl. Sub-clinical DIC was diagnosed in case of a coagulation assay abnormality in the absence of clinical signs. Coagulation assay test was carried out every week following response to treatment. Flowcytometry for myeloid series had been performed on the bone marrow prior to the start of treatment. Cytogenetic study using the high resolution GTG banding method for documenting t(15,17) was utilized before the start of therapy.

Supportive care

Platelet and packed cell transfusion were given so as to maintain platelet and hemoglobin concentrations at levels above 50,000 mm^3 and 10 gr/dl, respectivelyCeftazidime, vancomycine and amphotericin-B were used if fever and neutropenia developed. Heparin was never used for prophylactic treatment of DIC but in case it occurred, FFP was transfused by the routine method and continued until the abnormality was corrected. For monitoring the effect of ATRA, the peripheral blood smear and bone marrow aspiration was checked every other day and every two weeks. Complete response to ATRA is defined as a complete maturation in the myeloid series and a decrease in the promyelocytes and myeloblasts below 5% of nucleated non-erythroid bone marrow cells. Partial response means partial differentiation and decreased promyelocytic granule to 5%-25% of nucleated non-erythroid bone marrow cells. The criteria of response to intensive chemotherapy are similar to that of AML patients. Overall survival, disease- free survival and early death were estimated by the Kaplan Meier method. The frequency of risk factors for early death or retinoic acid syndrome was compared using the chi-square test.

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Results

Translocation[15, 17] was found to be positive in 7 out of 8 patients. Median WBC count was 1,450/mm^3 at the onset of ATRA therapy (min: 300/mm^3, max: 4,4000/mm^3). Median period of ATRA therapy was 23.6 days (min: 4 days, max: 40 days). Complete maturation of myeloid series was seen in 22 patients (73.3%) and 8 patients (26.7%) showed partial or absence of maturation. The mean maturation time was 24.6 days (SD=7.1 days, min: 12 days, max: 37 days). During ATRA therapy hyperleukocytosis occurred in 19 patients and was found to be over 20,000/mm^3 and below 20,000/mm^3 in 16 and 3 patients, respectively. The coagulation disorder resolved between day 7 and 53. The mean time for normalization of this disorder was 23.4 days (SD: 14.7 days). Retinoic acid syndrome and hyperleukocytosis was seen in 12 patients. Mean WBC count in patients with and without retinoic acid syndrome was 1164/mm^3 and 1733/mm^3 respectively with a significant difference between the two groups ($p<0.01$). Increased expression of CD13, CD33 and CD34 did not have any effect on the incidence of retinoic acid syndrome. The other adverse effects of ATRA which did not have any relation to the retinoic acid syndrome were bone pain, headache, increased liver enzymes, increased triglyceride and erythema nodosum, dry skin, skin ulcer and desquamation. Thrombotic complications were seen in the form of deep vein thrombosis, and pulmonary embolism in 5 patients. The mean time for occurrence of retinoic acid syndrome was 11.3 days after initiation of ATRA therapy (SD=9.4 days, min: 1 days, max: day 30). Eight patients responded to dexamethasone and 4 patients received dexamethasone plus chemotherapy. On the whole, 10 patients responded to this treatment. During the study, 5 patients (30%) died due to severe infection with prolonged neutropenia and DIC in accordance with the retinoic acid syndrome was seen in 3 patients. The average follow-up period was1.5 years(min: 2 months, max: 30 months). After30 months of follow-up, a total of 19 patients (67%) were found to be in complete remission.

Discussion

All-*trans* retinoic acid is a subgroup of the retinoid family, which cause differentiation and apoptosis of immature malignant promyelocytes. It affects retinoic receptors and retinoid target genes in both normal and malignant promylocytes.[13,14] The promyelocytes with t (15, 17) are more sensitive to ATRA. In different studies complete remission rate was 90% but relapse was always seen if chemotherapy had not been used.[15] Intensive chemotherapy after complete maturation with ATRA causes long-term survival and cure in 25 to 50 percent of all patients.[15,17] In recent studies the incidence and severity of hemorrhage has decreased by the use of ATRA therapy. ATRA, however, can sometimes be fatal. In the preliminary studies carried out by the Frankel group, the incidence of retinoic acid syndrome was23% of all cases. At present the early use of chemotherapy and dexamethasone has decreased the incidence of this syndrome. In this pilot study, 70% of all patients reached complete remission and 30% died due to treatment failure. Retinoid syndrome was seen in 12 patients (35% of cases). However, 10 out of these 12 patients recovered later. There was a significant correlation between leukocytosis before treatment and the incidence of retinoic acid syndrome. Median time of occurrence of retinoic acid syndrome was on day 11. There was no correlation between increased expression of CD 13 and the incidence of retinoic acid syndrome. Complete maturation by all-*trans* retinoic acid was seen on day 24.4 and the median time in which the coagulation disorder was treated on day 23.4. The other complications of all-*trans* retinoic acid were not as severe as those of the retinoic acid syndrome and were subsequently treated. Skin ulcer and other dermatological complications were observed in 34.3% of patients and were accordingly treated. The major causes of mortality were infection and DIC. International studies of APL patients referred between 1994-97 show that the complete remission rate, the 4-year event-free survival rate, and 4-year overall survival rate was 80%, 96%, 62% and 77%, respectively. When chemotherapy was used alone, complete remission rate and 4-year overall survival rate was 40%. In combination with chemotherapy, ATRA has a higher complete remission rate and a longer survival rate in APL patients. ATRA also decreases the incidence of hemorrhage and early mortality caused by chemotherapy. The basic mechanism of the effect of ATRA depends on the presence of t(15, 17) and

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the abnormal retinoic acid receptor. A high-dose retinoid and specially ATRA induces differentiation by acting on the retinoid target genes. Combined chemotherapy with ATRA and anthracycline-Ara C , has shown a higher rate of complete remission in APL.[20] As seen in other studies, this study also shows that induction or maintenance therapy with ATRA, produces an improvement in both the disease-free and overall survival of patients with newly diagnosed acute promyelocytic leukemia.

This study shows that ATRA therapy is safe for the treatment of acute promyelocytic leukemia. As seen in other studies[21], this improves both disease-free survival and overall survival when compared with chemotherapy alone. It causes differentiation and apoptosis of malignant promyelocytes but never eliminates the leukemic clone. In order to destroy the leukemic clone, intensive chemotherapy is required following complete maturation of the malignant clone by ATRA. They cause a higher rate of complete remission and long-term survival. We therefore recommend the use of all-trans retinoic acid for induction therapy followed by intensive chemotherapy in all patients with acute promyelocytic leukemia.

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