

All-transretinoic acid and chemotherapy in the treatment of acute promyelocytic leukemia

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Abstract

BACKGROUND: All-transretinoic acid (ATRA) and chemotherapy has improved complete remission rates and disease free survival in acute promyelocytic leukemia (APL). There is scanty data from Middle East. **AIM:** To determine the efficacy of ATRA and multi-agent combination chemotherapy in treatment of APL in a single Centre in Kuwait. **SET-UPS AND DESIGN:** Tertiary cancer centre, retrospective study. **METHODS AND MATERIAL:** All newly diagnosed APL patients were treated with oral ATRA 45mg/m² daily until complete remission (CR), intravenous daunorubicin 50mg/m² on days 1,3 and 5, cytosine arabinoside 100mg/m² 12hrly on days 1 through 10 and etoposide 100mg/m² on days 1 through 5. Post remission three courses of intensive consolidation chemotherapy were administered. Since October 1999, maintenance chemotherapy consisting of oral 6 mercaptopurine 90mg/m² daily, methotrexate 15mg/m² weekly and ATRA 45mg/m² for 2 weeks every three months was added. Complete remission rates and duration, relapse rate and toxicity were studied. **RESULTS:** 22 of 24 evaluable patients (91.6%) achieved CR. The median duration of remission was 13 months (range 2-55 months). Three patients (12.5%) relapsed. Two patients (8.3%) developed retinoic acid syndrome and responded to dexamethasone. Five patients (20.8%) died one each of refractory disease, during remission induction and of relapse. Two patients died while in remission. **CONCLUSION:** ATRA and combination chemotherapy results in high complete remission rates and low relapse rate in newly diagnosed APL. Maintenance therapy may be useful in preventing relapses.

Key Words: Acute Promyelocytic Leukemia, All-transretinoic acid, Chemotherapy, Kuwait.

Introduction

Treatment of acute promyelocytic leukemia with All-transretinoic acid produced high CR rates but was attended by potentially fatal retinoic acid syndrome and high relapse rate.¹ Sequential combination chemotherapy following initial treatment with ATRA, resulted in CR rate of 91% and relapse rate of 31%.² Combination of ATRA + chemotherapy resulted in lower relapse rates but similar CR rates at 2 years compared to ATRA followed by chemotherapy.³ This suggested an additional or synergistic effect of ATRA and chemotherapy on reducing the incidence of relapse in APL, which was

optimal when the two treatment modalities were administered together. Use of maintenance therapy including ATRA and low dose chemotherapy has been shown to further reduce relapse rate.^{3,4}

We report results of ATRA and combination chemotherapy in APL patients treated in a single center in Kuwait.

Materials and Methods

Patients of acute promyelocytic leukemia diagnosed at Kuwait Cancer Control Centre from March 1997 to April 2003 were retrospectively studied. All patients

diagnosed were studied and no case was excluded. All patients had given written informed consent for treatment.

Treatment schedule: Induction therapy consisted of ATRA 45mg/m²/day divided into two doses administered every 12 hours, until CR and for a maximum of 90 days along with daunorubicin 50mg/m² slow IV push day 1, 3 and 5, etoposide 100mg/m² IV over 1 hour days 1 - 5 and cytosine arabinoside 100mg/m² 12 hourly IV push day 1 - 10 according to MRC AML10 protocol. Bone marrow was examined 17-21 days post chemotherapy. After restoration of absolute neutrophil counts to $1 \times 10^9/l$ and platelets $>100 \times 10^9/l$ -consolidation chemotherapy was started.

Consolidation chemotherapy was based on modified MRC AML 10 protocol and consisted of course 1, daunorubicin 50mg/m² IV days 1, 3 and 5, etoposide 100mg/m² IV over 1 hour days 1-5 and cytosine arabinoside 100mg/m² IV 12 hourly days 1-8.(ADE 8)

Course 2: Daunorubicin 50mg/m² IV days 1 and 2, etoposide 100mg/m² IV over 1 hour days 1-5, cytosine arabinoside 200mg/m² IV continuous infusion days 1-5 (ADE 5) **or** IV mAmsa 100mg/m² on days 1-5, etoposide 100mg/m² IV over 1 hour on days 1-5 and cytosine arabinoside 200mg/m² continuous infusion days 1-5 (MACE).

Course 3: Mitoxantrone 10mg/m² IV over 30 minutes days 1-5, cytosine arabinoside 1gm/m² IV over 3 hours 12 hourly days 1-3.(MidAC)

Maintenance therapy: consisted of oral ATRA 45mg/m² in two divided dose for 2 weeks every 3 months, oral 6 mercaptopurine 90mg/m² daily and oral methotrexate 15mg/m² every week for a total of two years.

Treatment of coagulopathy: Coagulopathy was treated with fresh frozen plasma / cryoprecipitate until resolution and random platelet transfusion to maintain platelet count $> 20 \times 10^9/l$. Heparin was not used.

Patients with suspected ATRA syndrome were treated with dexamethasone 10mg IV 12 hourly for at least 3 days and ATRA was discontinued.

Evaluation of response: Complete remission was defined as normalisation of peripheral blood counts (platelets $>100 \times 10^9/l$, absolute neutrophil count $>1 \times 10^9/l$) and a normocellular bone marrow with $<5\%$ blasts.

Failure was defined as inability to achieve CR. Patients

who died during or after induction chemotherapy who did not have a bone marrow examination were considered to be treatment failure. Remission duration was defined as the time from attainment of CR to relapse, death during CR or to last follow up while in CR. Relapse was defined as presence of $>5\%$ leukemic promyelocytes or blasts in the bone marrow, or appearance of leukemic cells in the peripheral blood or central nervous system. Toxicity profile was determined on the basis of physical examination, chest X-rays, electrocardiogram and determination of left ventricular ejection fraction by multigated radionucleotide scan. Biochemical screening was performed before treatment and at least twice weekly during chemotherapy, toxicity was graded according to WHO criteria. ATRA syndrome was defined according to Frankel et al.⁵

Study end points

Complete remission rates and duration, relapse rate and toxicity were studied.

Results

Twenty-eight newly diagnosed patients of APL constituting 21.5% of the total 130 adult patients of acute myeloblastic leukemia were studied. One patient was induced with ATRA alone, three patients left, two on day 4 of treatment and 1 on day 28 for further treatment abroad. 24 patients were evaluable. The patient characteristics are given in table 1.

Twenty of the 24 patients achieved CR after first induction chemotherapy (83.3%) and 2 patients achieved CR after 2nd induction chemotherapy resulting in overall CR of 91.6%. One patient had refractory disease and was taken off protocol. One patient died on

Table 1: Patient Characteristics

Total No. of patients	: 24
Males / Females	: 18/6
Median age in years (range)	: 40 (17-55)
Fever	: 13/24
Bleeding	: 17/24
Median WBC x 10 ⁹ /l (range)	: 6.3 (0.8 - 120).
WBC $>10 \times 10^9/l$: 7
Median platelet count x 10 ⁹ /l (range)	: 28 (9-126).
Median hemoglobin g/dl (range)	: 8.2 (4.2-12.9)
DIC	: 12/24
FAB subtype - M3 typical	: 20
M3 variant	: 4

day 10 of treatment. Twenty-one patients received 'ADE8' combination chemotherapy. One patient was treated with Daunorubicin only along with ATRA because of toxicity. Twenty patients received MACE/ADE5 combination chemotherapy. Nineteen patients received MidAC. One patient did not receive MidAC block because of congestive cardiac failure.

The median duration of CR was 13 months, range 2-55 months. Three patients relapsed at 5, 7 and 31 months respectively. Two patients achieved second remission and maintained CR at follow up of 30 and 41 months respectively. The remaining patient died before further antileukemic therapy could be administered.

All twelve patients after October 1999 were administered maintenance therapy. Six patients have completed maintenance therapy; all twelve patients are in first CR. Coagulopathy was corrected in all patients at median of 5 days (range 2-8 days). Of the 24 patients, five patients died. One during remission induction, one of refractory disease, one in relapse and two in remission.

All patients were evaluated for toxicity. Majority of the patients had either grade I or II toxicity, mainly mucositis, vomiting and diarrhoea. Renal, hepatic and cardiac toxicity was seen in occasional patient only. 62 febrile neutropenic episodes were encountered. 52% episodes were fevers of unknown etiology, 29% were clinically documented and 19% of the episodes were microbiologically documented.

ATRA syndrome occurred in two patients (8.3%), both patients responded to intravenous dexamethasone and discontinuation of ATRA.

Discussion

In the present study ATRA and combination chemotherapy was used for remission induction in APL patients and 91.6% achieved CR. This is similar to the results in large multicenter trials, 91% in APL91, 92% in APL93, 95% in the Italian and 89% in the Japanese trials.^{2,3,6,7} These CR rates were superior to 69%-81% CRs obtained with chemotherapy alone.⁸ CR in patients with WBC > 10 x 10⁹/l was 71.4%, compared to CR rates of 50-70% reported in literature.^{2,3} In view of high relapse rate after treatment with ATRA alone or ATRA and low dose maintenance chemotherapy,^{1,8} consolidation chemotherapy is an essential component of treatment of APL. In the present study 3 courses of consolidation chemotherapy were administered

consisting of anthracycline, cytarabine and etoposide in two courses and anthracenedone and intermediate dose of cytarabine in one course. Recent studies have shown that cytarabine may be omitted without compromising CR or disease free survival,^{4,9} however, high dose cytarabine consolidation may be useful in patients with minimal residual disease detected by PCR.¹⁰ Molecular studies were not available in our center and intermediate dose cytarabine may have contributed to improved outcome in our patients.

In the present study, at a median follow up of 13 month (range 2-55 months), 3 patients (12.5%) relapsed. None of these patients had received maintenance therapy. These results are comparable to those obtained in other studies.^{3,4,9,11} Two patients achieved 2nd complete remission with ATRA and chemotherapy. The patients were in 2nd CR at 30 and 41 months of follow up. In the APL91 trial all of the 10 patients initially treated with ATRA who relapsed and were retreated with ATRA achieved a second CR.^{2,8} Arsenic trioxide has produced high rates of second complete remission in relapse following ATRA and intensive chemotherapy and has emerged as the treatment of choice.^{12,13}

Use of intermittent ATRA, 6-mercaptopurine and methotrexate maintenance therapy has been shown to reduce the risk of relapse.^{3,4,14} In a randomized study the risk of relapse was 11% in the maintenance group compared to 27% in the no maintenance group.³ In the present study maintenance therapy was given to twelve patients and none has relapsed so far.

The incidence of ATRA syndrome has varied from 6% to 27% in various studies.^{15,16} In the present study ATRA syndrome occurred in 8.3% patients. The patients responded to dexamethasone and discontinuation of ATRA and no mortality was encountered. De Boltton et al found higher risk of relapse in-patients who developed ATRA syndrome.¹⁶ Interestingly both of our patients with ATRA syndrome relapsed.

In conclusion, combination of ATRA and chemotherapy in the remission induction of APL resulted in high CR rates. The use of consolidation chemotherapy reduced the risk of relapse and additional maintenance ATRA and oral chemotherapy further reduced the risk of relapse.

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