NEW HORIZONS

Acute Promyelocytic Leukemia : Experience at a North Indian Tertiary Care Hospital with Review of Literature

Vikas Agarwal, Arun Srivastava, Sunil Dabadghao, Soniya Nityanand

Abstract

Acute promyelocytic leukemia (APL) is characterised by balanced translocation between the long arms of chromosome 15 and 17 resulting in formation of fusion protein PML/RARα. Due to this abnormal fusion protein, myeloid cell differentiation is arrested at the promyelocyte level. This molecular defect and myeloid cell differentiation arrest can be overcome by pharmacologic doses of all-trans retinoic acid (ATRA). APL most commonly presents as catastrophic bleeding manifestations which is a major cause of mortality. If diagnosed and treated early, patients can be salvaged and can achieve long term disease free survival. Our experience of seven patients is presented. All patients presented with bleeding manifestation and two died due to it. Rest of the five patients who underwent chemotherapy in the form of induction with ATRA along with supportive measures (fresh frozen plasma and platelets) followed by consolidation therapy in the form of multi-agent chemotherapy, achieved prolonged disease free remission. Thus with early diagnosis and start of ATRA, APL is a potentially curable malignancy.

Key words

All-trans retinoic acid, Retinoic acid syndrome, Disseminated intravascular coagulation, RARα.

Introduction

Acute promyelocytic leukemia (APL) accounts for 5-10% of all the cases of acute myeloid leukemia (AML). One of the most significant advances in the field of oncology has been the understanding of the molecular mechanism responsible for the development of APL and for the therapeutic efficacy of all-Trans Retionic Acid (ATRA) in APL. Prior to the era of ATRA, APL was fatal in majority of cases with a cure in only 20-40% cases. However, with the use of ATRA, almost 80-90% cases can acheive complete remission (CR). In this article we are presenting our experience of seven patients with APL and review of recent literature.

Clinical Presentation

Clinically, APL present at a younger age in comparison to the other subtypes of AML and commonly with manifestations of disseminated intravascular coagulation (DIC). The usual presenting manifestations of AML such as hepato-splenomegaly, generalised lymphadenopathy or bone tenderness are less frequently seen (table 1).

From the Department of Clinical Immunology, Sanjay Gandhi Post Graduate Institute of Medical Sciences Lucknow (UP) India.
Correspondence to : Dr. Soniya Nityanand, Associate Professor, Deptt. of Clinical Immunology, SGPGIMS, Lucknow (UP) India.

Table-1 Salient clinical manifestations at the time of presentation and response to therapy.

Age/Sex	DOD (Weeks)	Fever	Anemia	Bleeding	Lymph-adenopathy	Hepato-splenomegaly	Remission	Relapse
20/M	6	+	+	GIT	+	–	+	-
25/M	6	+	+	Hematuria	+	-	+	-
35/F	3	+	+	GIT, Intracranial, Vaginal	-	-	+	-
35/F	8	+	+	Intracranial, Vaginal	-	-	died	NA
35/F	3	+	+	GIT Vaginal	-	+	+	-
46/M	3	+	+	GIT	-	-	+	-
32/M	4	+	+	Intracranial	-	+	died*	NA

*Died before start of therapy, (+) Yes, (-) No, (NA) Not applicable, DOD Duration of disease

Most of the cases have either normal or low leuckocyte counts; only a small fraction of cases, i.e. microgranular variant, may have leukocytosis. Paradoxically, DIC is exacerbated by chemotherapy. High early mortality has been reported due to intra cranial hemorrhage (1-4) varying from 8-47% in various series (3,4). Our limited experience of 7 patients over 4 years (1995-1999), clearly showed bleeding manifestations as the most common presenting symptom, seen in all. Four patients presented with gastrointestinal and 3 with intracranial bleeds. In addition, minor bleeds from genito-urinary tract were seen in 4 patients. All the patients were young (mean age 32.2 years) with male to female ratio of 4:3. All but one patient had normal or decreased leukocyte counts and 4 had deranged coagulation parameters. All the patients had bleeds out of proportion to their platelet counts. Hepato-splenomegaly and/or lymphadenopathy were seen in 2 patients.

Pathophysiologic basis of APL

During normal cell differentiation, ATRA in combination with retinoic acid receptors induces dimerization of the latter with subsequent binding to promotor sequences of various cell differentiating genes, resulting finally in myeloid cell differentiation. Another protein, promyelocyte leukemia (PML) protein, is not only important for cell differentiation but is also an important molecule in the different apoptotic pathways (5,6). Cells from mice lacking PML protein have been shown to be resistant to apoptosis induced by various agents like tumor necrosis factor, Fas, gamma interferon, ceramide and irradiation (5). Acute promyelocytic leukemia is a distinct subset of acute myeloid leukemia, characterised by balanced reciprocal translocation between long arms of chromosomes 15 and 17. This translocation results in fusion of portions of promyelocytic leukemia gene (PML) with retinoic acid receptor alpha gene (RARα) resulting in a fusion protein (PML/RARα) in 99% of cases. Other combinations of retinoic acid receptor alpha with promyelocyte leukemia zinc finger (PLZF/RARα), nucleophomin (NMP/RARα) and nuclear mitotic apparatus (NuMA/RARα) have been reported. RARα is a DNA binding transcription factor that, in conjunction with its cofactor, RXR, regulates myeloid differentiation; interference with the formation

of RARα-RXR dimers by the fusion protein PML-RARα in acute promyelocytic leukemia could block differentiation at the promyelocytic stage. The development of a leukemia closely resembling APL in PML-RARα transgenic mice strongly supports the pathogenic role of the fusion protein in the human disease. (7) Promyelocytes contain procoagulant granules in their cytoplasm.

Diagnosis of APL

As most of the patients of APL present with catastrophic hemorrhage, urgent diagnosis and intensive supportive care is required to avoid possible death. Earlier the diagnosis is established and treatment started, more favourable will be the outcome. Though the confirmation of diagnosis requires genetic testing or molecular studies, which may be delayed, initial decisions should be based on morphologic and cytochemical evaluation of the bone marrow smears, which should be available within hours. Morphologically, two variants; hypergranular form and microgranular form are reported. Hypergranular form is more common (75%) and promyelocytes stain positively with Sudan black and peroxidase stains. The cytoplasm of these cells demonstrate purplish granules with abundant auer rods. The microgranules variant presents with higher TLC and atypical promyelocytes and is seen in around 25% cases. The false negativity and positivity rates for APL, based on morphology and cytochemistry, are 1-2% and 5-10% respectively (8). Thus all patients diagnosed as APL on morphology should be administered ATRA as it rapidly ameliorates the coagulopathy and far outweights the potential risk of complications due to ATRA in a non-APL patient. Various newer techniques like RT-PCR, PML-immunostaining or Fluorescent in situ hybridization have shown promising results in confirming the diagnosis of APL in patients with normal karyotype on cytogenetic evaluation.

TREATMENT

Induction Therapy

Conventional chemotherapy (anthracycline based) has been reported to achieve 60-80% CR in patients with APL. The major draw back of chemotherapy is high (10-20%) early mortality due to bleeding diathesis (9) and neutropenic fever. Five year survival has been reported to range between 35-45% in various series (10-12). The use of ATRA alone as inducing agent has resulted in CR as high as 70-94% (13-15). The major advantages is rapid resolution of coagulopathy, no neutropenia and thus <5% early mortality. The question of inducing a patient with ATRA alone vs ATRA plus chemotherapy has been addressed in many trials with results favouring the use of a combination regimen (16). However, ATRA alone has been proposed as agent of choice for induction in poor risk patients. Despite the effectiveness of ATRA in causing differentiation of the leukemic cells, a small fraction of patients continue to die of bleeding complications. Before the advent of ATRA, DIC caused by release of procoagulant factors from the dying leukemic cells was responsible for the catastrophic bleeds and high mortality. Readily availability of standard supportive measures like plasma, cryoprecipitates and platelets has also helped significantly in decreasing the mortality rates. The major disadvantages of use of ATRA is its toxicity i.e. retinoic acid syndrome. It is characterised by fever, dyspnea, weight gain, pulmonary infiltrates and hyperleucocytosis. It occurs in around 25-30% of patients and is associated with high mortality. Pathophysiologically it involves the release of cytokines from APL cells and adhesion of such cells to capillary endothelium (17). However, early recognition (daily weight charting for weight gain and respiratory rate measurement for tachypnea) and use of dexamethasone (19) along with cytoreductive therapy has curtailed mortality to <5% at most of the centres of the world.

The ATRA syndrome is now quite rare (incidence <5%, death rate <0.1%) (8). The most common side effect of ATRA in our study was deranged liver function tests, seen in three patients, headache and skin desquamation in one each. None of the patients experienced retinoic acid syndrome.

Consolidation Therapy

Once complete remission has been achieved by induction therapy, maintaining it by judicious use of least toxic but most effective chemotherapy regimen remains a challenging issue. Earlier reports of high dose anthracylines curing few patients is no longer justified as the toxicity is unacceptably high. The efficacy and toxicity of anthracyclines, Ara-C, or combination of various other drugs have been variably reported (19-21). There is no consensus at present as to which regimen is most effective and least toxic. Various consolidation regimens used by different centers worldwide are shown in Table-2. Apart from these, recent reports of high dose Ara-C (3gm/m/^{2} q 12 h × 8 doses) and mitoxantrone (20) in one trial and low-intensity anthracycline consolidation followed by combined ATRA/chemotherapy maintenance therapy in another trial has shown promising results (22). The role of autologus or allogenic bone marrow transplant during consolidation (23,) or even during first relapse (24,25) is not favoured due to high toxicity and transplant related mortality and as results of chemotherapy are superior. We treated patients with ATRA alone during induction followed by 3-5 consolidation cycles with daunorubicin and standard dose Ara-C (100mg/m^2/24 hours), at 4-6 weekly intervals. There were 2 deaths during induction, both due to uncontrolled major bleeds and rest of the 5 patients achieved CR. The mean time to control bleeding manifestations was 7 days and mean time to achieve CR was 32 days. Of 5 patients who achieved CR, one relapsed after a period of 1.5 years, however he was successfully reinduced with ATRA followed by consolidation cycles and is presently in remission after 12 months.

Maintenance Therapy

There are now two large, recently published studies that support a role for maintenance therapy in APL (16,26). Both the trials showed significant reduced risk of relapse during maintenance if treated with ATRA. However, combination of ATRA and chemotherapy was found to be superior to either drug alone in European ATRA 93 trial (26). The appropriate dose and schedule administration of ATRA during maintenance is unknown.

Table-2 Various consolidation chemotherapy regimes used at different centres

Indian GIMEMA study	US Canadian inter group (on going)	European APL group
(i) Ara-C 1 gm/m^2/day, days 1-4 + Idarubicin 5 mg/m^2/day, days 1-4	Daunorubicin 50 mg/m^2/day, days 1-3+ATRA 45 mg/m^2/day, days 1-7 (2 cycles)	(i) Daunorubicin 60 mg/m^2/day ×3, days 3-5+Ara-C 200 mg/m^2/day ×7, days 3-9.
(ii) Mitoxantrone 10 mg/m^2/day, days 1-5+VP-16 100 mg/m^2/day, days 1-5	or Arsenic trioxide 0.15mg/kg/day ×25 days (2 cycles) followed	(ii) Daunobubicin 60mg/m^2/day ×3 + Ara-C 200 mg/m^2/day ×7
(iii) Idarubicin 12mg/m^2/day, Day 1+Ara-C 150 mg/m^2/day q8h SQ days 1-5+6-Thioguanine 70 mg/m^2/day, days 1-5	by : Daunorubicin 50mg/m^2/day, days 1-3 + ATRA 45mg/m^2/day, days 1-7 (2 cycles)	(iii) Daunorubicin 45 mg/m^2/day ×3 + Ara-C 1gm/m^2 Xq 12h ×8 doses

This is a critical issue as resistance to ATRA due either to metabolic inactivation or acquisition of mutations in the PML/RARα molecule can develop during long term administration (27). As CNS is a sanctuary site for APL and high levels cannot be achieved by conventionally administered ATRA, extramedullary CNS relapse has emerged as a significant problem (28).

New Therapeutic Agents

New formulations of ATRA are being developed and tested clinically with promising results. Exact place of these analogues in the therapy, as of today, remains unclear. Arsenic trioxide has been recently shown in Chinese studies to be effective as a salvage treatment for APL (8). Since then it is emerging as an effective therapy for relapsed and refractory APL patients. In one of the trial from Memorial Sloan Kettering, 11 of the 12 patients with refractory APL achieved hematologic CR after one course of arsenic trioxide and 8 ultimately showed molecular remission. However, the duration of CR was short lived and 3 patients relapsed while on therapy (29). Similar results have been reported by other studies as well. The mechanism of action of arsenic trioxide is induction of apoptosis independent of PML/RARα. Arsenic has been shown to induce degradation of PML/RARα protein and also induce post translational modification of the PML/RARα molecule by Ubiquitin like molecule called SUMO-1. (8) Whether ATRA and arsenic trioxide can be combined safely and, if so, will their effects be synergistic or antagonistic is being investigated. The concern that degradation of PML/RARα by arsenic may antagonise ATRA induced differentiation of the leukemic cells is controversial. However, in animal models of APL, the combination of ATRA and arsenic trioxide has shown synergistic results (30). Thus, clinical trial combining the two agents need evaluation in humans.

Summary and Future Directions

In this review, we have tried to highlight the progress made in the therapy of APL in last decade and also some of the current controversies regarding the choice of optimal drug and its duration at different stages of the disease. At present, besides high leukocyte count at presentation, no other molecular or clinical paramenter exists which can define the risk of relapse and thus need for more intensive chemotherapy. The future trials need to answer the risk stratification guidelines and tailoring of therapy. Development of a sensitive, quantitative, and technically reproducible assay to measure leukemia burden before, during and after completion of therapy and treatment guidelines as per it will be another challenge. Finally, it is hoped that with better insight into the pathogenesis of APL and rational drug discovery, safer and more effective therapies, not only for APL but other less curable hematologic maligancies will be available.

To conclude, all of our patients had presented with catastrophic bleeding manifestations and very low general condition. However, due to rapid diagnosis and early start of ATRA along with intensive supportive care, CR was achieved in 5 out of the 7 patients. Thus, APL is a potentially curable maligancy.

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