A RELAPSED ACUTE PROMYELOCYTIC LEUKEMIA TREATED WITH ARSENIC TRIOXIDE ALONE: CASE REPORT

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Abstract

Acute promyelocytic leukemia is now the most curable subtype of acute myeloid leukemia in adult .It is characterized by 3 main features which are the presence of abnormal promyelocyte in bone marrow, the occurrence of disseminated intravascular coagulopathy and the presence of classical chromosomal translocation {t(15:17)(q22:q21)} or its variant.

The incorporation of ATRA in the induction over the past 25 years represents one of the most important advances in treatment of AML by inducing more differentiation of leukemic cells into mature granulocytes giving higher complete remission rate and resolution of the life threatening coagulopathy as well as decreases the relapse rate in comparison with chemotherapy alone.

In 1990's, investigators from China reported that arsenic trioxide (ATO) induces complete remission (CR) in patients with relapsed or refractory APL in 90% of cases by inducing partial differentiation & apoptosis of leukemic cells.

In Al-Kadhimiya Teaching Hospital, we faced such a case of APL who relapsed for second time within 1 year duration of a previously achieved remission, and fortunately we treat the patient with ATO alone that induced CR within 1.5 month duration of treatment then followed by consolidation courses and maintenance treatment to strengthen this remission state that is still existing.

Keywords: myeloid leukemia, acute promyelocytic leukemia, M3 subtype, relapse, all-transretinoic acid, and arsenic trioxide.

IRAQI J MED SCI, 2006; VOL. 5 (2):97-101

Introduction

Thirty-one years old female patient who is a married housewife diagnosed as a case of acute promyelocytic leukemia in June 2001 on the base of clinical picture and hematological investigations.

She received classical induction chemotherapy regimen (7 and 3 regimen), which included Ara-c 100 mg/m^2/day (180 mg/day i.v. infusion in 500 ml DW 5% over16-18 hours) and anthracyclin (doxorubicin) in a dose of 45 mg/m^2 (80 mg/day) i.v. infusion in DW 5% in one hour) together with ATRA (all trans retionic acid) capsules in 45 mg/m^2 dose (60 mg/day). The latter was continued for the subsequent 2 m.o. She passed in first remission and received consolidation chemotherapy with ara-c &doxorubicine.

On July 2002, she returned back with early relapse of her disease, a new course of chemotherapy plus ATRA decided to be given similar to first course, but the results was partial remission that necessitated re-induction chemotherapy using 2 cycles of mitoxantran 20 mg/day i.v. infusion in day 1 and Etoposide 100 mg/day i.v. for 3 days.

Remission achieved but on August 2003, the patient re-presented with full blown picture of relapsed disease and considered to be 2nd relapse where decision taken to start supportive treatment as well as using, for the first time in Iraq, a new agent therapy for relapsed cases of APL which is[(Trisenox ®), arsenic trioxide]alone without the use of chemotherapy (according to literatures) in a dose of 0.15 mg/Kg/day (12 mg/day) as i.v. infusion for 3 hours continuing daily until achievement of new remission which occurred at 44th dose of treatment where all hematological parameters were corrected (table 1), hand by hand with careful and close observation for the anticipated adverse effects of this agent

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Received:21st February 2006, Accepted:10th May 2006

by repeating electrolytes study, coagulation screen, CBC and ECG monitoring.

Table 1: Follow up of WBC count and differential in this patient

Days of Rx	WBC	Neut.	Lymph	Promyel.	Blast	Notes	B.M.
On Dx	4.5x10^9/L	45%	46%	2%	1%		33% Promyelocytes 5% Blast
1ST	3.6 x10^9/L	41%	35%	16%	4%	Starting Trisenox 0.15 mg/Kg/day	
14th	10.7 x10^9/L	10%	14%	51%	6%	8%Myel. 6%Metamyel.	
18th	10.8 x10^9/L	35%	17%	23%	2%		
27th	4.0 x10^9/L	35%	51%	1%	1%		
32nd	2.6 x10^9/L	60%	31%	1%	zero		
44th						Stop treatment (Complete remission)	5%promyel. 2%blast
Follow up	9.6 x10^9/L	56%	35%	Zero	Zero		
	4.2 x10^9/L	57%	34%	Zero	Zero		
	3.2 x10^9/L	52%	43%	Zero	Zero		
	2.0 x10^9/L	32%	58%	Zero	Zero	Flu like illness	
	7.0 x10^9/L	60%	30%	Zero	Zero	On maintenance treatment	
	7.0 x10^9/L	79%	13%	Zero	Zero		

One month later she received consolidation course of (Trisenox ®) for 3 weeks only in the same dose 12 mg/day by infusion over 3 hours for 5 doses/week, to be followed by intensification chemotherapy and then subsequently by maintenance chemotherapy since that time which includes the following drugs:

1. ATRA every 3 m.o. for 15 days in dose of 45 mg/m^2
2. 6 MP 100 mg/ day
3. MTX 25 mg/ week

She is doing fine till the time of reporting the case on the 5th of October 2005.

Historical Background

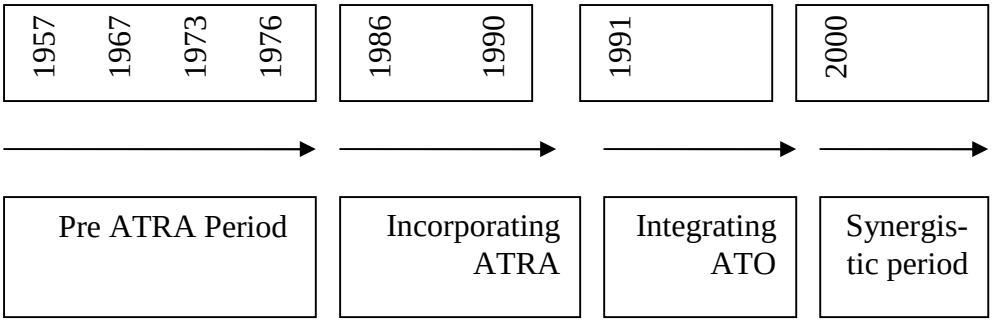
Leif Hillestad[1], the Swedish author, was the first who give the name of acute promyelocytic leukemia (APL), he concluded in 1957 that APL seems to be the most malignant form of acute leukemia. In 1976, the FAB groups assign this disease as M3 subtype of AML.

Also in 1976, a consistent chromosomal change, the balanced reciprocal translocation between the chromosomes 15&17 [t (15; 17)(q22:q21)] was reported by Rowley et al [2]. So far, APL has been shown to be characterized by 3 features: **1.** Presence of abnormal accumulation of promyelocytes in the bone marrow. **2.** The occurrence of afibrinoginemia and DIC that is reversed by chemotherapy, and **3.** Presence of the classical chromosomal translocation or its variant.

The past 3 decades has shown great advances in evolving therapeutic approaches for APL. In the 70s, the APL was treated by chemotherapy &was considered the most devastating subtype of AML. The

introduction of all transretinoic acid (ATRA) and arsenic trioxide (ATO) by Chinese hematologist since mid 1980s opened a new page in the history of leukemia therapy. ATRA is a derivative of vitamin A; which has improved the complete remission (CR) rate and long-term survival of APL patients [3]. On the other hand, the application of ATO further improved the clinical outcome of refractory or relapsed APL [4,5].

Lately, a higher quality remission and survival in newly diagnosed APL were achieved when ATRA was combined with ATO as compared to either monotherapy making APL a curable disease [6]. So the history of APL could be subdivided into 4 periods: pre ATRA period, incorporating ATRA, integrating ATO, and synergisting targeting period.



Since 1996, a large number of reports have shown that ATO induces a CR in 85%to 90% of patients with both newly diagnosed and relapsed APL [7,11,12].

Furthermore, after CR is achieved by ATO, molecular remission (i.e. negative for PML- RARα transcript detected by RT-PCR) is obtainable either with ATO or with ATRA and chemotherapy as a consolidation treatment[9].It seems likely that ATO used in the post remission therapy could prevent recurrence and achieve a longer survival time[8,9].

Mechanism underlying ATO triggered APL cell apoptosis, have been broadly studied. The apoptosis inducing effect is associated with down regulation of Bcl-2[10] which correlates with PML- RAR to block neutrophil differentiation [11].

Role of Arsenic trioxide (As_2O_3):

Investigators from china reported that arsenic trioxide induces CR in patients with relapsed and refractory APL in 90% of cases[4,5,9] (Table 2). Although the mechanisms have not been completely described, preclinical studies suggested that As_2O_3 induces partial differentiation and apoptosis of leukemic cells.

Soignet et al., initiated a pilot study of 12 patients with relapsed APL who were treated with Trisenox® (As_2O_3) at doses ranging from 0.06 to 0.2 mg/Kg/day until leukemic cells were eliminated from the bone marrow as determined by light microscopy (Table 3). 11 patients obtained CR with 8 of the 11 patients who initially tested positive for PML/RAR α fusion transcript later becoming negative (Table 4) [8, 9].

A multicenter trial of 40 patients confirmed the high CR (85%) (9)(Table 3), furthermore, approximately 78% of patients had no evidence of leukemic clone by PCR after 2 courses of Arsenic trioxide (Table 4)[8,9].

The most important toxicities include prolongation of the QTc interval and APL differentiation syndrome. However, two recent reports of sudden cardiac death with (Trisenox ®) indicate that careful monitoring is warranted.

Currently, Arsenic trioxide is considered to treatment of choice for

patients with relapsed disease, particularly in patient exposed to ATRA within the prior 12 months.

Table 2: Patients with relapsed and refractory APL achieving complete response after one course of arsenic trioxide therapy

Study, year	Number	No. CR	%CR
Zhang et al, 1996	42	22	52
Niu et al, 1999	47	40	85
	25	24	96
Soignet et al, 1998	12	11	92
Soignet, 2001	40	35	85

Table 3: Summary of results of 2 trials

Type	Trisenox dose Mg/Kg/day	CR	Time to BM remission (median)	Time to CR (median)	18 m.o. survival
Single center trial (Soignet et al) (N=12)	0.16 (0.06-0.2)	11 (92%)	32 days	54 days	67%
Multicenter trial (N=40)	0.15	34 (85%)	35 days	59 days	66%

Table 4: Cytogentics after As_2O_3 therapy in 2 studies

Type	Conventional cytogentics t (15;17)		RT-PCR for PML/RAR α	
	Absent	Present	Negative	Positive
Single center pilot CR cases=11	8 (73%)	1 (9%)	8 (78%)	3 (27%)
Multicenter trial CR cases=34	31 (91%)	0 %	27 (79%)	4 (12%)

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