Treatment of Acute Promyelocytic Leukemia with Single Agent Arsenic Trioxide: Experience from a Tertiary Care Center in India

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Abstract APML is a highly curable hematological malignancy which is treated with differentiation agents and chemotherapy. The morbidity caused by chemotherapy in the treatment of APML is a great cause of concern. We treated 12 patients with newly diagnosed APML with single agent arsenic trioxide between 2010 and 2014 irrespective of risk stratification. Out of 12 patient 2 patients died during induction. All the ten patients who completed induction, completed their consolidation and maintenance without any delays. One out of these ten patients relapsed 10 months after treatment. The remaining nine patients (80 %) are in molecular remission and are under regular follow up. The toxicity with arsenic was negligible and was very well tolerated. Hence arsenic trioxide as single agent can be offered as a standard alternative regimen to ATRA based chemotherapy in patients with economic constraints.

Keywords APML · Arsenic trioxide · Molecular remission

Background

Acute promyelocytic leukemia (APML) is one of the highly curable hematological malignancies with cure rate in excess of 80 % [1]. APML is caused by of reciprocal translocation between PML gene on chromosome 15 and retinoic acid receptor alfa (RAR α) on chromosome 17 [2].

APML is traditionally being treated with combination ATRA (differentiating agent) and chemotherapy [3]. The morbidity and mortality due to chemotherapy and cost involved in treatment is a matter of great concern in resource limited setting [4].

Arsenic trioxide (ATO) was being used in the treatment of relapsed APML with good results [5, 6]. This agent is recently being used as monotherapy in treatment of APML, irrespective of the risk stratification with encouraging results [4]. Hence it was decided to use single agent ATO in patients with APML who could not afford ATRA based regimen.

Method and Methodology

We retrospectively analyzed data of APML patient treated at Kasturba Medical College, Manipal with single agent ATO, between 2011 and 2015. The patient's demography, clinical feature at presentation, treatment given and toxicity profile were compiled by reviewing patient's hospital record.

Diagnosis of APML was confirmed on the basis of FISH or RT-PCR for PML–RAR α transcript. Patients were categorized to high, intermediate and low risk according to Sanz score for predicting relapse risk [7]. ATO was offered as standard alternative treatment in patients who could not afford ATRA based regimen after explaining clearly the

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benefit which can be expected in different risk stratified groups.

Arsenic trioxide was administered as a 3 h intravenous infusion in 500 ml 5 % dextrose. During induction chemotherapy, blood counts were monitored daily. Prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen level, thrombin time (TT) were monitored 3 times a week until stable, then weekly once. In case of derangement of PT/APTT, fresh frozen plasma was given (15 ml/kg) and in case of prolonged TT or low fibrinogen cryoprecipitate was given. The abnormal tests were repeated every day till normalization of the values.

Electrocardiogram was monitored for QT prolongation twice weekly as were renal, liver function tests, serum calcium, serum phosphorous and serum magnesium levels. During induction arsenic trioxide 10 mg was given intravenously daily till patient attains complete hematological remission (CHR) or 60 days whichever was earliest. Complete hematological remission was defined as absolute neutrophil count of $\geq 1.5 \times 10^9/\text{L}$, unsupported platelet count of $\geq 100 \times 10^9/\text{L}$ for 2 consecutive days or an unsupported platelet count of $\geq 100 \times 10^9/\text{L}$ for 15 consecutive days in the presence of leucopenia along with bone marrow examination with $<5\%$ blasts and promyelocytes. Hydroxyurea was given to patients presenting with high total count till the counts were stabilized according to schedule used by Mathews et al. [4].

During induction chemotherapy packed red cell was transfused to maintain hemoglobin $>8\text{ gm/L}$, platelets were transfused to keep platelet count $>30 \times 10^9$ and cryoprecipitate was given to maintain fibrinogen $>150\text{ mg/dl}$.

Following confirmation of CR, consolidation was given for 4 weeks followed by 6 courses of maintenance with 10 days a month of arsenic trioxide [4]. For both consolidation and maintenance same dosing and method of administration was used as discussed earlier.

Bone marrow examination and RT PCR for PML–RAR α transcript was done at the end of induction, prior to starting consolidation and before 1st, 3rd and 6th maintenance courses. After completion of treatment it was performed once in 3 months for 3 years and once in 6 months for next 2 years.

During course of treatment toxicity was carefully monitored and documented according to CTCAEv3.0.

Results

Between 2011 and 2015 total of 12 patients with 9 males and 3 females were treated with single agent ATO. The last patient in this study was initiated on treatment in March, 2014 with follow up of 11 months. The base line characteristics of all 12 patients is showed in Table 1.

The median duration of follow up of the study cohort was 28 months (range –11 to –43.2). The mean age of presentation was 36.42 years (SD 15.3) with youngest patient being 18 years and oldest being 60 years. Among 12 patients 3 patients belonged to good risk, 6 intermediate risk and 3 poor risk. 8 patients out of 12 presented with bleeding manifestation including 2 patients with disseminated intravascular coagulation and one patient with intracranial bleeding. Median haemoglobin, total count and platelet count was 7.2 gm/dl (range 4.6–9.5 gm/dl), 3800/dl (range 800–39,300/ μL) and 13,500/dl (range 5000–80,000 $\times 10^3/\mu\text{L}$) respectively. Median duration of induction was 40.92 days (SD 14.79) and hydroxyurea was given for mean duration of 15.82 days (SD 6.33). The median packed red cell, random donor platelets and cryoprecipitate during induction treatment were 9.5 units, 22.83 units and 8 units respectively. The median duration to achieve CR, status of follow up of all 12 patients are shown in Table 2.

During induction treatment 2 patients had differentiation syndrome, which was diagnosed with the presence of any three or more of the following signs which included weight gain, respiratory distress, radiographic opacities, pleural or pericardial effusion, hypotension, renal failure in the absence of other causes. These patients were treated with dexamethasone and both patients recovered fully. In one patient ATO had to be stopped temporarily for 3 days before restarting after control of differentiation syndrome.

Out of 12 patients 10 patients were able to complete induction and bone marrow was in remission in all 10 of them. All of them had RT PCR negativity for PML–RAR α transcript on bone marrow aspirate at the end of induction. One of patient who was of intermediate risk died on day 22 of induction due to candida sepsis and the other patient belonging to good risk died on day 4 of induction treatment due to pneumonia and respiratory failure. All the 10 patients who successfully completed induction treatment, completed consolidation and maintenance treatment without any delay. One among these 10 patients who was of intermediate risk, 10 months after the completion of treatment relapsed and declined any further treatment and expired after 3 months. Interestingly all 3 high risk patients in our study were able to tolerate ATO well without toxicity and all of them are in molecular CR and are under regular follow up.

The side effect profile of arsenic trioxide was very encouraging. One on patient who also was a diabetic had grade 2 peripheral neuropathy during maintenance phase of APML treatment. This was managed symptomatically without reducing the dose of ATO. 2 patient developed grade 1/2 hepatotoxicity and none of the patient developed grade 3 or 4 hepatotoxicity. None of the patients experienced grade 3 or 4 neutropenia.

Table 1 Base line characteristics of patient

PT. no	Age/sex	Hb (gm %)	TC ($\times 10^6/L$)	PLT ($\times 10^9/L$)	Risk	BM (Blast +PM) in %
1	18/M	7	2100	5	INT	77
2	31/M	5.1	21,200	18	High	92
3	37/M	5.4	1100	58	Good	71
4	19/M	7.9	800	11	Intermediate	89
5	49/F	5.5	3000	49	Good	95
6	24/F	9.5	1700	15	Intermediate	84
7	44/M	7.4	3200	6	Intermediate	86
8	51/F	4.6	39,300	12	High	89
9	18/M	8.2	4000	17	Intermediate	94
10	29/M	8.4	6400	10	Intermediate	75
11	40/M	9.1	22,900	12	High	90
12	60/M	7	7100	80	Good	95

Table 2 Response to ATO, time for CR, status OG last follow up

PT. no	Induction response	Days to CR	Differentiation syndrome	Completed treatment	Status at follow up	Days of hydroxy urea
1	CR	47	No	Yes	CR	24
2	CR	50	Yes	Yes	CR	13
3	CR	57	No	Yes	CR	18
4	CR	39	No	Yes	Relapsed and died	0
5	CR	39	No	Yes	CR	24
6	Early death	22	No	No	Died	22
7	CR	53	No	Yes	CR	11
8	CR	47	No	Yes	CR	19
9	CR	38	No	Yes	CR	14
10	CR	51	No	Yes	CR	13
11	CR	49	Yes	Yes	CR	13
12	Early death	4	No	No	Died	3

Discussion

APML accounts for 10 % of all AML cases in adults [8]. It is characterized by reciprocal translocation between PML and RAR- α gene on chromosome 15 and 17 respectively. ATRA and Anthracycline based chemotherapy has been the standard of treatment for APML resulting in 70–80 % 5 year overall survival [1]. The major problem with this treatment has been chemotherapy induced morbidity and mortality and the cost involved in treatment [4].

Arsenic trioxide has been traditionally used for the treatment of relapsed APML [5, 6]. ATO is a differentiating agent and in a dose dependent manner causes apoptosis of promyelocytes [9]. This agent has been shown to be cost effective and compared to chemotherapy had a friendly toxicity profile [4].

In our study, we treated 12 patients of APML with single agent arsenic trioxide which included 3 patients of

good risk, 6 patients of intermediate risk and 3 patients of poor risk APML. We encountered 2 induction death. The remaining 10 out of 12 patients (83.3 %) achieved hematological CR. All these 10 patients had molecular CR at the end of induction but one among them relapsed 10 months after the completion of therapy. The remaining 9 patients continues to be in molecular CR under regular follow up. The induction death and induction CR'S in our study was comparable to study by Mathews et al. [4].

In our study all the 3 patients of high risk APML, responded to ATO therapy and were in haematological and molecular CR at the end of induction. All 3 patients successfully completed scheduled treatment and under regular follow up. This is contrary to study by Mathews et al. [4] where there were more induction deaths in high risk group. The encouraging results in high risk group patients in our study may be biased by smaller number of patients and shorter follow up.

The median time to achieve hematological CR was 40.92 days. Our results are comparable to in the study by Mathews et al. [4] where median time for hematological CR 43 days. But in the study by Ghavamzadeh et al. [10] the median duration was only 30 days. In our study hydroxyurea was used to reduce the count for a mean duration of 15.82 days.

The toxicity profile with arsenic trioxide in our study was encouraging. We encountered differentiation syndrome in 2 patients and both of them were treated with dexamethasone. In the study by Ghavamzadeh et al. [10] 13.2 % of induction death was due to differentiation syndrome [10]. There was no grade 3 or 4 neutropenia/hepatotoxicity encountered. None of the patients had increased QTc interval or other cardiac morbidities. Similar friendly toxicity profile is quoted by Mathews et al. [4]. This is contrary to some of the earlier studies where hepatotoxicity was of great concern when treated with ATO [11].

Consolidation chemotherapy with arsenic trioxide was given as day care basis without any complications and all the patients completed consolidation treatment without any delay.

In the present era where APML is highly curable hematological malignancy, our focus should be on reducing treatment related long term toxicities and to give good quality of life to these cancer survivors. Hence our focus should be to move away from chemotherapy and to treat APML with only differentiating agents.

The most encouraging result in this direction was from recently published study by Lo-Coco et al. [12] where ATRA and ATO has emerged as new standard of care in the treatment of low and intermediate risk APML compared to ATRA and chemotherapy in terms of friendly toxicity profile, better event free survival and overall survival. But in patients who could not afford ATRA based regimen, our study has shown that ATO as single agent can act as excellent alternative regimen. However larger studies and long term follow up with ATO is required before considering it as standard of care.

Compliance with Ethical Standard

Conflicts of interest None.

Human and Animal Right Statement All procedures performed in study involving human participants were accordance with ethical standards of the institution and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standard.

Informed Consents Received from all the study patients.

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