SHORT COMMUNICATION

Role of Arsenic Trioxide in the Management of Aplastic Anemia

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Abstract Aplastic anemia is a common problem in the developing world with therapeutic challenges as most of the patients are non-affording to standard care owing to resource constraints. We present the results of an open label single arm, non-randomized, single center, prospective phase II trial of the compassionate use of arsenic trioxide in patients refractory to ATG or unable to afford the standard of care therapy. The study was prematurely terminated at eighth week due to non-response in 100% of patients and death in two patients. The results are contradictory to what is already published and needs validation in a multicentric setting.

Keywords Aplastic · Anemia · Arsenic

Introduction

Aplastic anemia (AA) is a common problem in real world settings with the incidence in Asian population being 2–3 times higher than the western population. A study from Lucknow, India in pediatric population calculated the incidence at 6.8 per million [1]. The factors responsible for high incidence of AA in Asian countries including India are lower socioeconomic status, high exposure to pesticides, chemicals, toxins and pathogens [2]. Optimal management of severe aplastic anemia (SAA) remains a

challenge in the resource constraint settings. Majority of the patients in our setting lack medical insurance or sufficient finances to afford anti-thymocyte globulin (ATG) and/or allogeneic hematopoietic stem cell transplant (Allo-HSCT), therefore, the scope for the same remains limited. A sizable number of patients receive oral androgen and calcineurin inhibitors for treatment due to non-affordability resulting in a need for an affordable and efficacious alternative treatment of SAA. Studies from China showed remarkable results with arsenic trioxide (ATO) in relapsed/refractory SAA [3–5]. We initiated this prospective trial to study the outcomes of ATO therapy in Indian patients with SAA.

Patients and Methods

This is a single center, open labeled, non-randomized, single arm, prospective phase II trial. The study was approved by institutional ethics committee (IEC) vide NK/661/Res/2626 and was registered in Clinical Trial Registry India (CTRI) vide CTRI/2013/03/003480. Consecutive patients who were refractory to ATG based therapy or cannot afford standard therapy were enrolled for the compassionate use of ATO. None of the patients were eligible for Allo-HSCT. Arsenic trioxide was infused as 0.15 mg/kg/day as 1-h infusion on an outpatient basis either in the day care or at a center of convenience to the patient for five days in a week planned for a total of 12 weeks. Blood and platelet transfusions were given as per institutional protocol. Patients were monitored weekly in our clinic for response to therapy or any kind of toxicity (monitored by complete blood count; liver functions and ECG). Informed consent was obtained from all the patients.

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Results

We treated six patients of relapsed or refractory aplastic anemia with arsenic trioxide. All patients have been pretreated, the details of the therapy are enumerated in Table 1. The median age was 34 years (19–55 years) with male predominance (M:F: 2:1). Patients received ATO for a median duration of 42 days (35–48 days). All six patients tolerated ATO therapy well without any adverse events directly related to ATO. Four patients developed infectious complications during the study period. Two patients succumbed to severe infection. No significant improvement in cytopenias was noted at a median of 49 days (42–88). Bone marrow (BM) examination was repeated for one patient (patient no. 2) which showed persisting marked hypocellularity. The outcomes of these patients are mentioned in Table 1.

The study was prematurely terminated at eighth week as per IEC guidelines, owing to 100% non-response and deaths in two patients. The study was terminated after recruitment of six patients (this number was based on the number of patients which showed positive response in the previously published literature) [3].

Discussion

The pathogenic mechanisms behind the development of AA are incompletely understood. Immune mediated mechanisms may be responsible for disease in the subset of patients responding to immunosuppressive therapy. BM adipocytes are predominant negative regulators of the BM microenvironment leading to impaired hematopoiesis [6]. Thus, ablation of the BM adipocyte compartment induces osteogenesis, which in turn, promotes a more supportive environment for hematopoietic reconstitution [7, 8]. ATO significantly inhibits adipogenic differentiation and enhances MSCs osteogenic differentiation, thereby leading to improved hematopoiesis in SAA patients [9].

The options of second line therapy for AA includes a second cycle of ATG/cyclosporine (CSA), Alemtuzumab, or Eltrombopag [10]. There is no consensus regarding therapy for patients who do not respond to immunosuppression and are unable to undergo Allo-HSCT. ATO seemed to be an attractive option for therapy of relapsed/refractory disease [3–5]. The comparison of the current study with published literature is reckoned in Table 2. All patients in the reports by Li et al., Song et al., and Lin et al. have been treated with immunosuppression (at least CSA) at some point, whereas three patients in the current study were pretreated with danazol only [3–5]. Five out of six patients in the current study have received danazol. Such a treatment is not mentioned in published reports by other investigators

Table 1 Clinical details and the outcomes of the severe aplastic anemia patients managed with ATO

SN	Age/sex	No. of prior Rx	Name of regimen used previously	ATO therapy days	Toxicity	Outcome	Hb (g/dL)			WBC count (/ μ L)			Platelets (/ μ L)		
							Pre ATO	Post ATO	ATO	Pre ATO	Post ATO	ATO	Pre ATO	Post ATO	ATO
1	55/F	1	Danazol	45	–	Died of septicemia	5.8	5.3		2000	700		31,000	33,000	
2	22/M	3	hATG, rATG, CSA, Tacrolimus	42	Herpes zoster	No response, alive	4	6.1		1300	900		5000	7000	
3	34/M	1	Danazol	35	–	Died of septicemia	8.5	4		1200	1200		7000	2400	
4	45/F	1	Danazol	42	Rise in creatinine from 0.6 to 1.75 mg/dL	Alive	6.1	8.4		4600	2600		11,000	4000	
5	32/M	2	CsA, Danazol	45	–	Alive	3.7	6.6		2200	3000		5000	6000	
6	19/M	3	hATG, CSA, Danazol	49	Febrile Neutropenia, Oral candidiasis	Alive	6.7	6.6		2300	1200		10,000	10,000	

Blood transfusion and component support have been given to the patients with clinical indications for the same
hATG horse ATG, rATG rabbit ATG, CsA cyclosporine, M male, F female, Rx treatment, No number, Hb hemoglobin, ATO arsenic tri-oxide

Table 2 Comparison of our study with the published literature

	Song et al. [5]	Li et al. [3]	Current study
Population	China	China	India
Patients included	Relapsed/refractory AA	Relapsed/refractory AA	Relapsed/refractory AA
N	10	5	6
Treatment under study	ATO 0.15 mg/kg/day; 5/7 day/week + CsA	ATO 0.15 mg/kg/day; 5/7 days/week	ATO 0.15 mg/kg/day; 5/7 days/week
Median days of therapy	Not mentioned	43 (range 41–48)	42 (35–48)
CR	30%	60%	–
PR	70%	40%	–
No response	None	None	100%
Deaths	None	None	(33%)

AA aplastic anemia, N number of patients, CsA cyclosporine, CR complete response, PR partial response

[3–5]. Antagonistic effect of danazol on arsenic trioxide though not described, needs to be evaluated. There may be a difference in how SAA patients from different ethnicities respond to ATO, which can explain these differences [3–5]. Further studies in larger and more heterogeneous patient populations may explain these differences in response rates.

Conclusion

Our study did not replicate the results published in similar trials. In fact, there was no response to adequate duration of ATO therapy and the trial had to be terminated prematurely. In view of the negative results observed by us, there is a need to validate positive results reported by other groups at a much larger level in a multi-centric trial.

Author Contributions GP, AK, PM, SV performed the research; PM and YU analyzed the data and wrote the paper, and GP, PM, SV designed the research study.

Compliance with Ethical Standards

Conflict of interest None.

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