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REVIEW

Arsenic trioxide-based therapy in relapsed/refractory multiple myeloma patients: a meta-analysis and systematic review

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Abstract: Multiple myeloma (MM) is a clonal malignancy characterized by the proliferation of malignant plasma cells in the bone marrow and the production of monoclonal immunoglobulin. Although some newly approved drugs (thalidomide, lenalidomide, and bortezomib) demonstrate significant benefit for MM patients with improved survival, all MM patients still relapse. Arsenic trioxide (ATO) is the most active single agent in acute promyelocytic leukemia, the antitumor activity of which is partly dependent on the production of reactive oxygen species. Due to its multifaceted effects observed on MM cell lines and primary myeloma cells, Phase I/II trials have been conducted in heavily pretreated patients with relapsed or refractory MM. Therapy regimens varied dramatically as to the dosage of ATO and monotherapy versus combination therapy with other agents available for the treatment of MM. Although ATO-based combination treatment was well tolerated by most patients, most trials found that ATO has limited effects on MM patients. However, since small numbers of patients were randomized to different treatment arms, trials have not been statistically powered to determine the differences in progression-free survival and overall survival among the experimental arms. Therefore, large Phase III studies of ATO-based randomized controlled trials will be needed to establish whether ATO has any potential beneficial effects in the clinical setting.
Keywords: multiple myeloma, arsenic trioxide, clinical trial, therapy, meta-analysis

Introduction

Multiple myeloma (MM) is a clonal malignancy characterized by the proliferation of malignant plasma cells in the bone marrow and the production of monoclonal immunoglobulin.[1] MM, which is the most common primary tumor of the bone marrow, is an incurable tumor that occurs in 4.8 to eight per 1,000,000 in the US. It is estimated that 21,700 people in the US have suffered from MM, and deaths from the year 2012 numbered 6,020 people.[2] The majority of MM patients will relapse or become refractory to therapy after achieving complete remission.[3] Over the past decade, treatment for MM patients has been greatly improved due to autologous stem cell transplantation and new drugs (thalidomide, lenalidomide, and bortezomib). These management increased rate of complete response (CR) and subsequently extended survival both in young and elderly patients with MM.[3] MM patients usually achieved CR more quickly by using the new drugs, which was associated with longer survival. However, most patients eventually relapse after CR, indicating that residual tumor cells exist. Resistance to conventional therapy caused by residual diseases displays multifactorial characteristics, which are difficult to overcome by targeting one single mechanism.[4] Alternatively, identification of novel cellular targets or signaling pathways regulating myeloma cell

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growth would improve clinical outcome and survival in MM patients refractory to chemotherapy. Mitochondria, which have been implied to play a crucial role in programmed cell death, apoptosis, are found to be a promising drug target that may benefit MM patients or other tumor patients.[5–7]

Arsenic trioxide (ATO) is the most active single agent used in the treatment of acute promyelocytic leukemia (APL) patients (newly diagnosed and relapsed or refractory APL patients).[8,9] The rationale for ATO as a therapy for MM is that ATO inhibits cell viability, suppresses growth, and induces apoptosis in myeloma cells in an in vitro cell culture model.[10,11] Instead of affecting the extrinsic (receptor-mediated) apoptotic pathway, ATO was proposed to disrupt the intrinsic (mitochondria-mediated) apoptosis pathways by generating reactive oxygen species (ROS) and suppressing the reduced glutathione (GSH) cellular redox enzymes, GSH peroxidase and thiotransferase (glutaredoxin).[1,4] Due to multifaceted effects of ATO on MM cell lines and primary myeloma cells, Phase I/II trials have been conducted in relapsed or refractory MM patients with heavy pretreatment. However, the application of ATO has so far achieved limited success in relapsed/refractory MM,[12] which could be attributed to the acquisition of resistance in MM due to changes in GSH levels and apoptotic regulators or other unknown reasons.[12] In this study, we will review and update the published clinical studies as to the effect of ATO on MM in adults.

Methods

Search strategy and selection criteria

MEDLINE, PubMed, and Web of Science were searched in December 2013 using the search terms "arsenic trioxide", "multiple myeloma", and "clinical studies" and synonymous search terms such as "arsenite", "chemical LAND21", "myeloma", and "clinical trials". Studies identified through the approach as described were screened by titles first, then by abstracts of the publications. After exclusion of nonrelevant publications and identification of duplicates from the different databases, the remaining papers were evaluated in the full-text version for inclusion and exclusion criteria and for relevant articles in the reference lists. All clinical studies except case reports were chosen: eg, randomized controlled trials (RCTs), cohort studies, case control studies, and case series. The language of publication was restricted to English and Chinese. Only the studies containing 15 or more patients were eligible for inclusion. All searched data were retrieved. Authors' bibliographies and references of selected studies were also searched for other relevant studies. The most complete study was chosen to avoid duplication if same patient populations were reported in several publications.

Adult patients with progressive MM who were shown to have chemoresistant relapse and/or refractory MM were eligible for the study. The response of patients with MM to chemotherapy was determined according to criteria raised by Blade et al.[13] Briefly, CR was defined as negative myeloma protein in serum and in urine on at least two determinations for a minimum of 6 weeks, no increase in the size of lytic bone lesions, and $<5\%$ plasma cells in the marrow. Partial response (PR) was defined as a $\geq 50\%$ reduction in the level of serum M-protein on at least two determinations 6 weeks apart, reduction in 24-hour urinary light-chain excretion by either $\geq 90\%$ or to <0.2 g (if present), $\geq 50\%$ reduction in size of soft tissue plasmacytomas, and no increase in size or number of lytic bone lesions. Minor response (MR) was defined as 25%–49% reduction in serum M-protein, 50%–89% reduction in urine M-protein (if present), 25%–49% reduction in size of plasmacytomas, and no increase in size or number of lytic bone lesions. Progressive disease (PD) was defined as $>25\%$ increase in serum M-protein or in 24-hour urinary light-chain excretion, an increase in size or development of new existing lytic bone lesions, or plasmacytomas or development of hypercalcemia. CR, PR, and MR were considered responses to the treatment in terms of treatment effectiveness. All publications regarding in vitro/ex vivo studies, cell lines, and human xenografts were excluded. There were no restrictions on the types of interventions of ATO-containing therapy regimens, either as a single drug or in combination with other agents. Overall response rates (CR, PR, and MR) and probabilities for overall survival (OS) and progression-free survival (PFS), where applicable, will be included.

Data for study characteristics and clinical response were summarized and incorporated into table format. Heterogeneity of investigation was evaluated to determine whether the data of the various studies could be analyzed in a meta-analysis.

The database search generated 36 articles from PubMed and two from the Web of Science. After initial screening of all titles, abstracts, and eligibility, ten full-text studies were selected for more detailed assessment. A search of the article references did not produce additional publications. Eventually, ten publications met the inclusion criteria for qualitative study and two for meta-analysis. The article search and study selection are depicted in Figure 1.

Results

Response to, and efficacy of, ATO-based therapy

Eight of ten included intervention studies were designed as case series, and two studies applied ATO in an RCT setting.

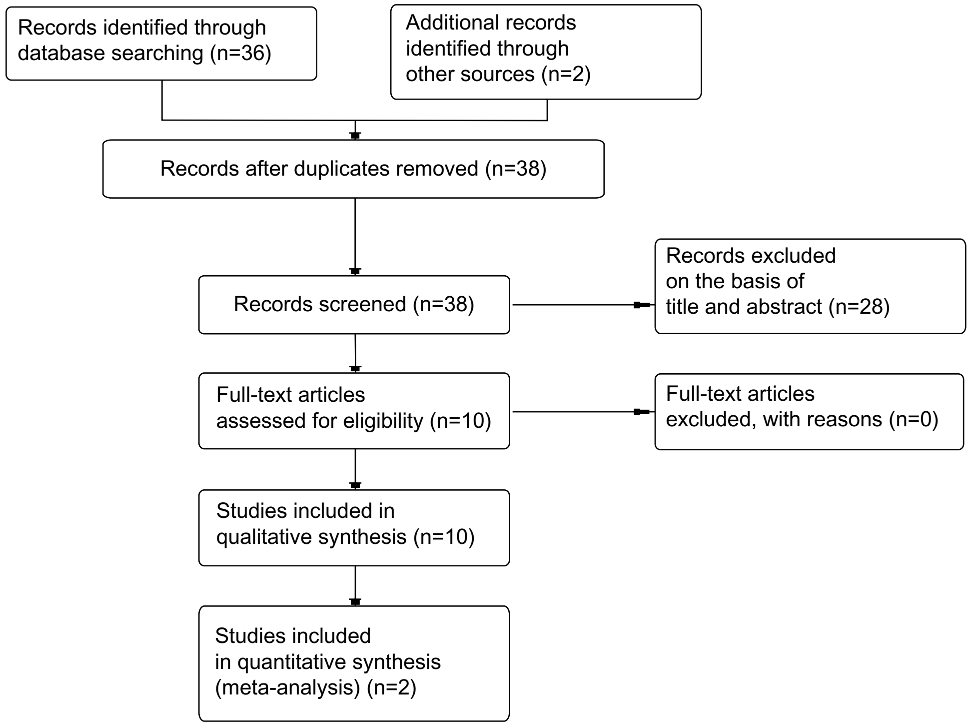

Figure 1 Flow chart of study selection.

All the trials recruited patients who suffered from progressive MM, defined as being either refractory to conventional therapy or in a relapsed state. The median age was from 50.8 years to 66 years. The number of patients ranged from 15 to 65. Studies containing fewer than 15 patients were excluded.[14–22] All studies were published between 2003 and 2012 and performed in both developing and developed countries. Therapy regimens varied dramatically as to the dosage of ATO and monotherapy/combinations with other agents available for the treatment of MM. ATO dosage varied from 0.125 mg/kg/day to 0.3 mg/kg/day. Only one study utilized ATO as monotherapy.[23] Other drugs utilized in combination regimens were ascorbic acid (AA), melphalan, dexamethasone, bortezomib, thalidomide, and doxorubicin. All ten studies utilized changes in the serum monoclonal protein levels to determine the response reaction (CR, PR, stable disease, and PD). Four investigations retrieved information as to the probability of OS and PFS.[24–27] Detailed features of the studies are described in Table 1. Two of the included studies with 77 patients investigated the association between ATO treatment and response to ATO-based therapy. A random effects model was chosen for analysis because of heterogeneity. The combined OR was 0.64 (95% confidence interval: 0.17–2.35; Z=0.68; P=0.5) (Figure 2), indicating that ATO treatment was not correlated with CR or PR in patients with advanced MM.

Safety and tolerability

All patients were evaluable for safety and tolerability. ATO-based combination therapy was well tolerated by most patients, but several significant toxicity events in heavily pretreated patients have been reported.[28] The adverse effects and their frequencies are listed in Table 2.

Discussion

ATO, a beneficial antineoplastic drug for MM,[29] has been identified to exert effects on myeloma cells through different molecular mechanisms.[30] Instead of inducing differentiation of myeloma cells as it did in APL,[8,9] ATO induces apoptosis and inhibits proliferation and angiogenesis in MM cells via various signaling pathways. First, ATO induces apoptosis by generation of ROS[31,32] and reduction of free GSH.[26] In contrast to triggering proapoptotic signaling pathways upstream of mitochondria, ATO acts directly on mitochondria to generate apoptosis.[4,33] ATO-associated combination of activation in ROS and inhibition in the GSH cellular redox systems seems to directly disrupt mitochondrial membrane potential and damage mitochondria of susceptible myeloma cells.[4,26] Second, in myeloma cells, constitutive STAT3 activation and upregulation of BCL-xL confer resistance to apoptosis and generate multidrug-resistant phenotype.[34,35] ATO inhibits interleukin-6-mediated phosphorylation of STAT3 and blocks early activation of JAK1 and JAK2 in

Table 1 Clinical trials of ATO-based therapy in relapsed/refractory myeloma patients

Reference	Regimen	Patients	PFS	OS	MR (%)	PR (%)	CR (%)	Comments
Hussein et al[48]	ATO 0.25 mg	24				33		Object response, ≥25% reduction in serum M-protein, is considered as PR
Yan et al[45]	ATO 0.14 mg/kg	21		47.6		42.9		
Abou-Jawde et al[27]	ATO 0.25 mg/kg + AA 1 g + dex 40 mg	20	316 days (10.5 months) in all patients 584 days in those with a response	962 (32 months) days		20	10	
Baz et al[49]	ATO 0.25 mg/kg + AA 1 g + dex 20 mg + thali 100 mg	16	9.4 months		0	31	0	
Berenson et al[26]	ATO 0.25 mg/kg + AA 1 g + mel 0.1 mg/kg	65	7 months	19 months	22	23	3	
Berenson et al[25]	ATO 0.125/0.25 mg/kg + AA 1 g + bortezomib 0.7/1.0/1.3 mg/m^2	22	5 months	>18 months	18	9	0	OS has not been reached yet with a median follow-up of 13 months
Wu et al[28]	ATO 0.25 mg/kg + AA 1 g + dex 40/20 mg	20	4 months	11 months	30	10	0	
Dey et al[23]	ATO 0.14 mg/kg	15			0	40	33	
Qazilbash et al[24]	Mel 200 mg/m^2 + AA 1 g + arm 1: no ATO, arm 2: ATO 0.15 mg/kg, arm 3: ATO 0.25 mg/kg	48	24 months			60	25	
Zhang and Bao[44]	ATO 0.14 mg/kg + dex 20 mg + thali 100 mg	29				85.7		

Abbreviations: AA, ascorbic acid; ATO, arsenic trioxide; CR, complete response; dex, dexamethasone; mel, melphalan; MR, minor response; OS, overall survival; PFS, progression-free survival; PR, partial response; thali, thalidomide.

the JAK/STAT3 pathway, known to promote cell survival.[36] Additionally, ATO activates JNK pathway in ATO-sensitive myeloma cells but not in ATO-insensitive/resistant myeloma cells, which might improve outcome in MM therapy.[37] In contrast, ATO activates the p38/MAPK pathway that contributes to resistance to ATO in myeloma cells.[38,39] Inhibition of NF-κB activation by ATO was observed to react with a critical cystein in the activation loop of IκB kinase.[40] Finally, ATO may also block vascular endothelial growth factor-mediated migration of myeloma cells and bone marrow neovascularization induced by NF-κB.[41] However, the ERK/MAPK and AKT pathways activated in myeloma cells are not affected by ATO.[42,43] ATO did not affect expression of BCL-xL either.[43]

The response of patients with MM to chemotherapy was determined according to criteria raised by Blade et al.[13] The results of the studies on effects and toxicities of ATO on MM patients were not consistent from different research groups. Most clinical trials found that ATO has limited effects on MM patients because of severe toxicity and less efficacy compared with other newly found drugs. ATO therapy, combined with AA and dexamethasone, causes significant toxicity in relapsed and/or refractory MM patients with heavy pretreatment, while the effects of ATO-based regimens are inferior to other new medication-based combination therapy such as bortezomib and thalidomide.[28] Although the results from the combination therapy with ATO, AA, and bortezomib in advanced MM patients are encouraging, MM patients fail to obtain significant benefit from ATO-involved combination therapy compared with that produced by monotherapy using a single drug.[25] In contrast, Zhang and Bao[44] reported that therapy with ATO, dexamethasone, and thalidomide causes minor toxicity in patients with relapsed and/or refractory MM, suggesting that ATO-based combination therapy is effective and safe for advanced MM patients.

Data variations among the studies, such as variation in dosage, treatment duration, make it incredibly difficult to conduct a quantitative analysis. Therefore, most results were described as narrative data. Two RCTs were eligible to be analyzed in a meta-analysis format (Figure 2).

In Table 1, we list ten examples of literature in the past 10 years with number of patients larger than 15. By comparing with the review by Rollig and Illmer,[1] we added two more recent publications, Zhang and Bao[44] and Yan et al.[45] We did not include literature containing fewer than 15 patients: eg, Hofmeister et al[14] and Borad et al.[17] A clinical trial conducted in Iran in 2011[22] only had 12 MM patients, which did not reach our criterion of 15, so we removed this publication from

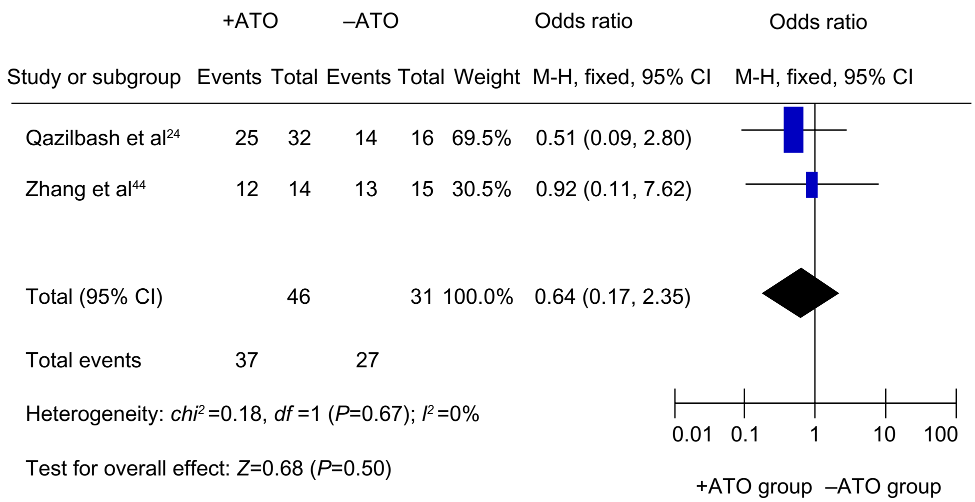

Figure 2 Forest plot showing the correlation between ATO application and clinical response to ATO-based therapy in advanced MM.
Notes: Two of these included studies with 77 multiple myeloma (MM) patients investigated the association between arsenic trioxide (ATO) treatment and response to ATO-based therapy. A random effects model was chosen for analysis because of heterogeneity. The combined odds ratio was 0.64 (95% confidence interval [CI]: 0.17–2.35; Z=0.68; P=0.5).

our review. A randomized Phase II trial[46] was also excluded because it focused on 58 patients to determine whether adding bortezomib to a preparative regimen of ATO, AA, and high-dose melphalan was safe.

One of the antitumor activities of ATO is due to the production of ROS. Not surprisingly, AA, which accentuates ROS, has been shown to enhance anti-MM effects in MM patients.[15] However, other studies discovered that AA may inhibit antitumor effects induced by ATO.[25,47] At present, there is no explanation for the discrepancy between studies from different groups. Therefore, large Phase III studies will be necessary to decipher effects of AA on ATO in the clinical setting. In one of the RCTs,[24] 16 of the 19 patients with advanced MM were randomized to ATO-based groups, and their PFS and OS were comparable with patients in the control group. Since the small number of patients (48 patients) was randomized to three different treatment arms, the small number of patients is not statistically powered to determine the differences in PFS and OS among the three experimental arms. Therefore, large Phase III studies of ATO-based RCTs will be needed to analyze whether ATO has any potential beneficial effects in the clinical setting.

Because of the relatively low incidence of MM, it is difficult to obtain a large number of patients in each clinical trial. Over the past decades, the numbers of the patients in a variety of trials vary from four to 65. Only two studies performed in 2008 and 2012 are qualified for quantitative meta-analysis. Actually, there is no fixed minimum number of studies required for meta-analysis, although the resulting effect size can be unstable due to a small number of studies. However, our meta-analyse obtains consistent conclusions compared with previous studies. Therefore, the analyzed data

Table 2 Adverse effects of arsenic trioxide-based therapy in relapsed/refractory myeloma patients

Reference	Hematological (%)			Nonhematological (%)					
	Anemia	Neutropenia	Thrombocytopenia	Cardiac	Gastrointestinal (diarrhea, vomiting, stomatitis)	Hepatic	Renal	Skin rash	Fever/ infections
Hussein et al[48]	9	17			79	25			33
Yan et al[50]		5		5		19	5		
Abou-Jawde et al[27]		5							
Baz et al[49]									
Berenson et al[26]	5	2		6	6	2	2		22
Berenson et al[25]			5	15					14
Wu et al[28]		20	10			15			50
Dey et al[23]									
Qazilbash et al[24]				6	52	2	6	4	23
Zhang and Bao[44]									

are meaningful and acceptable. Another purpose of our review is to draw to the attention of the researchers that a larger Phase III trial is urgently needed to obtain more solid data to accept or reject the present conclusions for ATO in MM patients.

Disclosure

The authors have declared that no competing interests exist in this work.

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