

Arsenic Trioxide in Patients with Refractory Multiple Myeloma: A Prospective, Phase II, Single-Arm Study

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Abstract- Multiple myeloma (MM) characterized by proliferation of plasma cells in bone marrow and production of monoclonal immunoglobulin's. Recently, arsenic trioxide (ATO), has been considered for treatment refractory MM. We assessed the safety and efficacy of ATO for patients with refractory MM. A phase 2, study of arsenic trioxide was conducted in 12 MM patients, whose refractory to two standard therapy. Patients received arsenic trioxide, 0.25 mg/kg/d for 5 d/week during the first 2 consecutive weeks of each 4-week cycle with 2 week rest. Patients who completed one 4-week cycle were evaluated for response to treatment. Twelve patients with refractory multiple myeloma received ATO. Disease assessment was based the amount of serum proteins electrophoresis. Of the 10 patients; stable disease was observed in four patients (33%), progression disease in five patients (41.6%), complete response in one patient (3.8%) and the remaining two patients could not be assessed for a response (because of increased liver enzymes after the first week). Some adverse events: increase liver enzymes and serum creatinine, neutropenia, pruritus, nausea, vomiting, lower extremities edema, noninfectious diarrhea was observed. These results indicate that ATO is active and well tolerated as a single-agent salvage therapy, even in patients with late-stage, refractory MM.

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Introduction

Multiple Myeloma (MM) is characterized by the clonal malignant plasma cells in the bone marrow, and production of monoclonal immunoglobulin's (1). Multiple Myeloma includes 1% of total malignancies and 10% of blood malignancy. (2-3) Mean age at the time of diagnosis is 68 years (4). Potential symptoms include increased infection rate, hematopoiesis disrupted, osteolytic lesions, pain and bone fractures, hypercalcemia, hyperuricemia, renal failure and blood clotting and hyper viscosity. Survival 5, 10 and 15 years in MM patients were 31, 10, is 4 percent (5). Despite several recent therapeutic advances, MM remains incurable; almost all patients eventually relapse and develop drug resistance. MM disease of patients older than 60 years and many patients actually can not tolerate heavy treatments. Current standard of care for relapsed or refractory MM includes glucocorticosteroids, salvage chemotherapy agents or combinations, thalidomide-based or bortezomib-based regimens or stem cell transplantation (6). High-dose chemotherapy with

autologous stem cell transplantation does not improve survival, but it may improve progression-free survival (7). Although survival has improved somewhat with these new treatment options, nearly all patients will develop resistant disease; thus, it is essential to provide patients with additional therapeutic options. IL-6 is one of the cytokines that released through myeloma cells. This cytokines with paracrine and autocrine effect produce growth and proliferation of myeloma cells. On the other hand, close contact of myeloma cells and tissue stromal cells produce large amounts of the IL-6 which, induce proliferation myeloma cells. Recent studies have shown that VEGF increased the bone marrow angiogenesis also; it has an effect on myeloma cells. VEGF causes proliferation and migration of myeloma cells. IL-6 that has been made by bone marrow stromal cells induced increase in VEGF level. On the other hand, VEGF increased IL-6 level through effects on stromal tissue and myeloma cells (7). White Arsenic or arsenic trioxide (ATO) was used by FDA in 2002 and in Europe for the treatment of recurrent or refractory APL cases (1). However, there has been little discussion about

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health effects of arsenic trioxide in malignant lymphoma cells and CML category and non hematologic malignancies such as liver and gallbladder tumors, cancer pancreas, kidney and prostate (8).

In one studies, ATO also has an effect on tumoral cells and stromal tissue. Through Caspase-9 it can stimulate apoptosis and proliferation of MM cells, unlike, to IL-6 that can inhibit effects of Dexamethason, anti-apoptosis effect of ATO can not inhibition by IL-6. On the other hand, ATO through the effect on microenvironment tissue of marrow, can reduce the connection between stromal cells and the myeloma cells and reduce production of VEGF, IL-6, so, anti-tumoral effects of ATO was increased. This drug can be improved, patients with refractory MM (8).

Berenson *et al.* reported, 29 percent of Multiple Myeloma patients after treatment with ATO showed 25 reductions in the M protein (9). Hussein *et al.* in another study were submitted 25 percent reduction in M protein in 8 patients (33 percent) and disease stabilization in 6 patients (25 percent) that use ATO (10). Munshi *et al.*, in a clinical trial with different dose of ATO had persistent therapeutic response in 2 patients (11). Rousselot *et al.* with the same dose in 1-3 weeks time reported stable disease and partial reduction in M protein levels (12). Other studies of arsenic have had positive results in combination with other drugs such as ascorbic acid, steroids and melphalan on refractory MM to check with that (10,13-15).

We assessed the safety and efficacy of ATO and evaluation, serum level of VEGF, IL-6 for patients with refractory multiple myeloma (MM).

Materials and Methods

Study design

This study was a phase II, prospective, single-arm study of arsenic trioxide in patients with refractory MM in Hematology-Oncology Research Center in Tabriz-Iran from 2007 to 2008.

Patient selection

Patients with diagnoses of refractory MM, Karnofsky performance status above 60, expected survival rate at least 3 months, lack of background other debilitating diseases were eligible for the study. Informed consent was obtained from all patients prior to entry into the study. Baseline clinical laboratory test includes routine hematology and clinical chemistry, including renal, liver thyroid function test, FBS, Mg, Ca, P, B2-microglobuline, VEGF, IL-6, and

the ECG. Patients with high creatinine, liver enzymes increased more than 3 times, heart disease or history of ischemic heart disorder in last 6 month or QT interval more than 0.45 second, uncontrolled diabetes, a serious infection, history of untreated Tonic seizure, granulocytes less than 1200/ml, platelets less than 100×10^9 , hemoglobin less than 10g/dl were excluded.

The levels of VEGF were determined by a specific enzyme-linked immunosorbent assay (IBL, Hamburg, Germany) with a detection limit of 20 pg/mL of VEGF. The levels of IL-6 were determined by a specific enzyme-linked immunosorbent assay (Bender MedSystems, Vienna, Austria) with a detection limit of 1.3 pg/mL of IL-6.

Study treatment

ATO administrated over 2 h as intravenous infusion at a dose of 0.25mg/kg/d, for 5 d/week for 2 weeks followed by no therapy for 2 weeks, in repeated 4-week cycle. ATO was manufactured by the Sina Pharmacy company, Tehran, Iran (10 ml vial containing 10 mg of drug). Patients received a maximum of six treatment cycles. Vital signs and symptoms of Patients review for allergic reaction during the infusion of ATO. Before in each treatment cycle; ECG was performed for QT interval control. At the end of the first and second weeks CBC, liver enzymes, electrolytes and serum creatinine levels were taken and at the end of the fourth week of each cycle, disease assessment for, reduce bone pain, complications occurred during treatment, the amount of serum proteins electrophoresis, β 2-microglobuline, VEGF, IL-6. If partial response to treatment or stable disease, treatment was maintained but for more serious complication such as long distance to QT, increased liver enzymes more than 3 times, creatinine higher than 2, allergic reaction, neuropathy or evidence in favor of disease progression and not to continue in our patient satisfaction, treatment was withdraw. Response to the treatment was based on the rate of decline of serum proteins electrophoresis during 4-week was defined.

Assessment of efficacy

Response to treatment was assessed by myeloma parameters (serum protein electrophoresis) at screening and 4 weeks after the last treatment. Developer Full Complete Response (CR): remove the M protein in electrophoresis.

Partial Response (PR): reduction of more than 50 percent of M protein in electrophoresis. Partial answer: Minor Response (MR) decreased from 25 to 49 percent protein M stable disease: less than 25 percent reduction

in serum M protein. Disease progression (Progression) or no response to treatment: more than 25 percent increase in serum M protein. SPSS version 13 was used for the analysis of the data. Pearson correlation coefficients were calculated for the evaluation of association between, serum protein electrophoresis, VEGF and IL-6.

Results

Patient characteristics

Twelve patients were enrolled in this study. 4 patients (33.3%) women and 8 patients (66.7%) were male. Patients ranged in aged from 38 to 75 years, with a median age of 58.66±12.09 years. Patient's demographics are summarized in Table 1.

Patient disposition

Of the 12 patients, 12 patients completed a course of treatment. Eight patients discontinued prematurely during cycle one because of disease progression (n=4). Increased liver enzymes (n=2), heart problem (n=1), increase in renal tests (n=1).

All of these eight patients were included in efficacy analysis and treated as non-responders for tumor response evaluation in order to avoid selection bias. Four patients received two or more cycles of therapy: two cycles (n=4), three cycle (n=3), four cycle (n=3), five cycle (n=2), six cycle (n=1). 2 patients died during the study.

Disease response

Responses to treatment, as defined by reduction in M protein, are summarized in table 2. Of the 12 patients; stable disease was observed in four patients (33%), progression disease in five patients (41.7%), complete response in one patient (8.3%) and the remaining two patients could not be assessed for a response (because of increased liver enzymes after the first week).

There is no significant relationship between the amount of serum proteins electrophoresis before and after ATO treatment. ($P=0.023$). Also, there is no significant relationship between the amount of serum proteins electrophoresis, with VEGF serum levels ($P=0.012$), and, with IL-6 levels before and after treatment ($P=0.23$). There is no significant relationship between VEGF and IL-6 before and after treatment ($P=0.012$). There is no significant relationship between the amount of serum proteins electrophoresis, VEGF, IL-6 and of β 2-microglobuline serum level before and after treatment ($P>0.05$).

Safety assessment

All patients (12) were evaluable for safety and tolerability of ATO. Most adverse events were mild to moderate (grade 1 and 2). One patient was increased liver enzymes another were increased creatinine. Symptoms such as swelling and redness in the skin lower limbs, nausea, vomiting, itchy, non-infectious diarrhea and pain was intensified with the treatment or spontaneous symptoms were resolved. None of patients had neuropathy or increased QT distance.

Table 1. Patient demographic

Patients	Age(year)/sex	Previous chemotherapy regimens	Karnofsky score	NO of ATO cycles
1	75/M	M+P, THAL	60	1
2	62/M	M+P, VAD	60	1
3	53/F	M+P, CTX+DEX	100	1
4	62/M	M+P, VAD	90	1
5	42/M	M+P, VAD, THAL	100	6
6	41/F	M+P, VAD	60	1
7	69/M	M+P, VAD	80	1
8	62/F	M+P, VAD	60	4
9	73/M	VAD, THAL	60	1
10	75/M	M+P, VAD, THAL	70	5
11	38/F	VAD, THAL	60	2
12	60/M	M+P, VAD, THAL	60	1

M=Melphalan, P=Prednisone, THAL=Thalidomide, AD=Vincristine+Doxorubicin+Dexamethason, CTX=Cyclophosphamide, DEX=Dexamethason, ATO=Arsenic Trioxide

Discussion

This study showed that arsenic trioxide as monotherapy in refractory Multiple Myeloma has therapeutic efficacy as a minimum to prevent disease progression. The study was originally designed to assess response rates in patients with refractory disease. All patients in the study were refractory to previous therapeutic regimens. Treatment refractory patients are extremely difficult. Manage of refractory patients are difficult, because they are unlikely to respond to further therapeutic manipulations. Arsenic trioxide single-agent therapy resulted in a clinical benefit in these poor-prognosis patients (1-2). In this study at the end of the first cycle 4 patients (33%) attained stable disease. One patient attained complete response (8%) and disease was progress in 5(41.6%) of patients. Finally, a patient (8%) who received 32 days of treatment had partial response and another patient received the full 60 days without specific symptoms, the disease was stable. In a study patient's treatment were continued for around 14 days a month, 25-49 percent reduction in M protein in 3 patients of the 10 patients and 4 patients were stable disease. Response to arsenic trioxide was gradual and occurred a median 67.5d of treatment (7). In clinical trial, the effect of ATO on 14 patients with refractory daily dose of 0.15mg/kg was study 60 days. Therapeutic response at the end of 3 patients was remarkable: 75 percent of the patients and another patient's 50 and 25 percent reduction were reported in M protein. In 8 patients, disease activity remained stable and 3 patients were disease progression (13). In a similar study with the same protocol on 24 patients resistant to medical treatment, the treatment period with an average 5.67 day, 33 percent partial response to treatment patients and 25 percent of patients were stable (17). Seems to increase cycle of treatment increased therapeutic response. Although the diversity protocols used in this patients and the low number of patients, so precise protocol is not possible with this medication. Therapy with arsenic trioxide was well tolerated with manageable adverse events. Neutropenia experienced in one a patient. However this neutropenia was not associated with an increased incidence of netropenic fevers or an increased use of growth factors. Also liver enzymes were increased in other patients only follow patients without complication. In this study, with repeated assessments of patients during treatment QT prolongation was observed. In other studies, Multiple Myeloma patients this complication has been reported (7-13). Three of the patients who were able to complete 3 cycles or more, reduction in the amount of B2-microglobuline were seen

that were not mention in other related studies. In this study, we didn't find any statistically significant relationship between VEGF, IL-6 and response to ATO, which is probably because of the number of the patients.

Overall, arsenic trioxide therapy did not compromise the patients' performance status and did not confer significant added toxicity. The clinical efficacy and favorable toxicity profile of arsenic trioxide demonstrated in this study argue for the further evaluating of arsenic trioxide in refractory multiple myeloma using new dosing strategies combined with the traditional chemotherapeutic agents, such as Melphalan and Dexamethason, or non-traditional agents, such as bortezomib and thalidomide.

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Arsenic trioxide in patients with refractory multiple myeloma

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