Arsenic Trioxide (Trisenox®) In Refractory or Relapsed Multiple Myeloma: Rationale and Clinical Efficacy using the MAC Regimen

[1,2]Berenson JR, [3]Boccia R, [4]Bessudo A, [5]Steis R, [6]Bozdech M, [7]Pomeroy JT, [8]Siegel D, [9]Flam M, [10]Moss R, [11]Stadtmauer E, [12]Lutzky J, [13]Lindgren T, [14]Patel R, [15]Volk J, [16]Jilani S, [17]Louie LA, [1]Ferretti D, [1]Purner M

[1] Inst. for Myeloma and Bone Cancer Research and [2]Oncotherapeutics, Inc. Los Angeles, CA; [3]Ctr. for Cancer and Blood Disorders, Bethesda, MD; [4]San Diego Cancer Ctr., Vista, CA; [5]Atlanta Cancer Care, Atlanta, GA; [6]Redwood Regional Onc. Ctr., Santa Rosa, CA; [7]Cancer Prevention & Treatment Ctr., Soquel, CA; [8]Med. Cancer Ctr., Hackensack, NJ; [9]Hem.-Onc. Med. Grp., Fresno, CA; [10]Fountain Valley, CA; [11]UPenn, Philadelphia, PA; [12]Mt. Sinai Compr. Cancer Ctr., Miami Beach, FL; [13] Hem.-Onc. Med. Grp., Orange, CA; [14]Compr. Blood & Cancer Ctr., Miami, FL; [15]Hem.-Onc. Ctr., Glendale, AZ; [16]Cancer Care Assoc. Torrance, CA, [17]CTI, Seattle, WA

INTRODUCTION

Resistance to chemotherapeutic agents such as melphalan, thalidomide, and the proteosome inhibitor bortezomib, is a common occurrence in multiple myeloma (MM) patients. Tumor cells develop resistance to these agents by increasing the production of survival factors and becoming insensitive to apoptotic signals. In MM, chemoresistance is associated with the constitutive activity of NFκB. Cell adhesion-mediated drug resistance plays also an important role in MM as interactions between MM cells and components of the bone marrow create a protective micro-environment. Therefore, effective treatment of refractory or relapsed MM patients requires agents that can restore apoptopic signaling in chemoresistant cells as well as in a chemoresistant microenvironment (1-3).

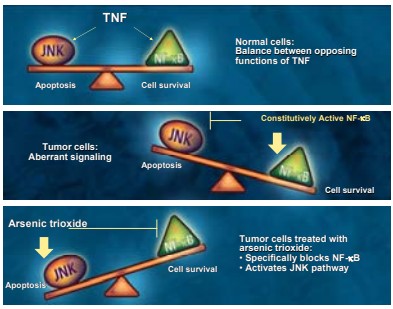
Two major pathways play a role in arsenic trioxide-induced apoptosis of malignant cells:

1. mitochondrial membrane depolarization and activation of downstream apoptotic pathways through the generation of reactive oxygen species;
2. specific activation of pro-apoptotic pathways through inhibition of NF-κB and activation of JNK.

In normal cells, NF-κB activity is tightly controlled by several regulatory proteins: in unstimulated cells, NF-κB is sequestered in the cytoplasm through binding with its inhibitor, IκB. Following activating signals, IκB is targeted for ubiquitination and proteasomal degradation through phosphorylation by an upstream kinase, IKKβ. Once released from IκB, NF-κB translocates to the nucleus. Arsenic trioxide interacts with IKKβ, thereby disrupting the NF-κB-signaling pathway.

The ligand/receptor pairs of the TNF family activate signalling pathways that regulate both cell survival and proliferation as well as apoptosis. The balance of these opposing functions determines ultimate cell fate. TNF-induced activation of NF-κB promotes cell survival. TNF-induced activation of JNK signalling is associated with apoptosis; however, activated NF-κB inhibits this pathway. Activation of the JNK pathway modulates the apoptotic process in a stimulus-dependent manner, facilitating both pro-apoptotic and anti-apoptotic outcomes. Arsenic trioxide can activate JNK through TNF, an upstream regulator of JNK. *In vitro* studies showed that JNK activation and arsenic trioxide-sensitivity are dependent on the presence of oxidative stress, a potent stimulus of apoptosis (4,5).

Arsenic trioxide restores pro-apoptotic signalling pathways



Melphalan, arsenic trioxide, ascorbic acid (MAC)

Studies in mice carrying human MM melphalan-resistant tumors, the combination of arsenic trioxide and melphalan markedly suppressed the growth of the tumor and significantly reduced serum paraprotein levels. Addition of ascorbic acid further improved the tumor activity of arsenic trioxide and melphalan combination treatment.

In a clinical pilot study, the combination of melphalan, arsenic trioxide and ascorbic acid was shown to be effective in the treatment of refractory and relapsed MM (6).

TREATMENT SCHEMA

Patients receive melphalan orally at a dose of 0.1 mg/kg daily for the first four days of each 6-week cycle. Arsenic trioxide is administered in a loading dose fashion at 0.25 mg/kg intravenously (IV, over two hours) followed by AA 1 gram IV over 15 minutes, during days 1-4 of the first week of each cycle. Following the first week, arsenic trioxide is administered at 0.25 mg/kg IV (over one hour) followed by AA 1 gram IV on a twice weekly schedule for the next four weeks of each cycle (weeks 2-5). Patients do not receive any study drugs during week 6. Disease assessments are done prior to the start of each subsequent cycle. Patients receive a maximum of six cycles of the treatment regimen.

Week	Arsenic Trioxide	Melphalan	Ascorbic Acid
1	0.25 mg/kg IV qd (d. 1-4)	0.1 mg/kg PO qd (d. 1-4)	1 gm IV qd (d. 1-4)
2-5	0.25 mg/kg IV twice weekly	None	1 gm IV twice week
6	rest	rest	rest

PATIENT DEMOGRAPHICS

Patient demographics (N=54)*	
Median age (years)	62 (range: 29-81)
Median number of failed therapies	3.5 (range: 1-8)
Patients that failed:	
Melphalan	16
Thalidomide or lenalidomide	29
Bortezomib	10
Peripheral stem cell transplant	11
Serum M-protein (g/dl)	
Mean	3.5
Range	range: 1.1-7.6
Urine M-protein (g/24h)	
Mean	1751
Range	35-11,733
B2 microglobulin	
Mean	6.2
Range	range: 0.5-25.9
Evaluable for efficacy	37
Too early to assess	9
Not evaluable#	8

*All patients had active progressive disease
#Did not complete one full treatment cycle

References

1. Aggarwal BB. Cancer Cell *6*: 203-208, 2004
2. Anderson KC et al. Cancer *J 8*: 12-25, 2002.
3. Hayashi T et al. Mol Canc.Ther *1*: 851-60, 2002.
4. Mak NK et al. Toxicol Lett.135:79-87, 2002.
5. Kajiguchi T et al. Leukemia.17:2189-95, 2003
6. Borad, et al. Leukemia.19:154–156, 2005.

PATIENT RESPONSES

Patient responses (N=37)	
Complete response (CR) (no serum M-protein)	0
Partial response (PR) (≥ 50% decrease in serum M-protein)	8 (22%)
Minor response (MR) (≥ 25-49% decrease in serum M-protein)	14 (38%)
Stable disease (SD) (change in M-protein ± 25%)	6 (16%)
Objective response (PR+MR)	22 (59%)
Disease control (PR+MR+SD)	28 (76%)
Objective responses in patients who failed:	
Melphalan	10/16
Thalidomide/lenalidomide	14/29
Bortezomib	7/10
PSCT	7/11

Improvement in serum creatinine (SCr) levels in patients with SCr ≥ 1.5 mg%

Baseline	Treatment	# of Cycles	Response
6.3	4.8 (-24%)	1	PR
5.7	1.6 (-72%)	1	MR
3.5	2.9 (-17%)	1	PD
3.2	4.3 (+34%)	2	PD
2.2	1.4 (-36%)	2	SD
2.2	1.4 (-36%)	2	MR
2.2	1.3 (-41%)	1	PD
1.9	1.5 (-22%)	2	MR
1.7	1.4 (-18%)	1	NA
1.7	1.8 (+6%)	1	MR
1.7	1.3 (-24%)	1	MR
1.6	1.3 (-19%)	2	MR
1.6	NA	on cycle 2	MR
1.5	1.5	1	MR

- **The MAC regimen resulted in objective responses in heavily pre-treated patients that had previously failed melphalan (RR=63%), thalidomide or lenalidomide (RR=48%), and bortezomib (RR=70%).**
- **Renal functioning improved while on MAC therapy: 14 evaluable patients had base line serum creatinine (SCr) ≥ 1.5 mg%; 10 of these patients had an improvement in serum creatinine levels, 7 of which had at least disease control with the treatment regimen.**
- **The median duration of response has not been reached; the range is currently 3+ to 13+ months.**
- **The median time to progression has not been reached; the range is currently 1+ to 13+ months.**

ADVERSE EVENTS

All patients were evaluable for safety:

- **The most commonly reported side effect was hematologic: grade 3 toxicity was reported in 12 patients, grade 4 in 2 patients; 41 patients received colony stimulating factors, 10 required platelet transfusions, and 10 required PRBC's**
- **11 patients experienced delays in treatment: 4 for blood counts, 2 for prolonged QT, and 5 for other reasons (elevation of LFT's, subdural hematoma, jaw pain with teeth extractions, sepsis) .**

SUMMARY

- **MAC is an active, steroid-free, regimen; responses were observed in patients that had failed multiple therapeutic regiments, including bortezomib.**
- **The MAC regimen has been well tolerated with few significant AEs reported.**
- **The MAC regimen did not induce neuropathy, patients with pre-existing neuropathy did not experience any worsening of their symptoms.**
- **Response to the MAC regimen was associated with an improvement in SCr levels in patients with renal insufficiency.**