A Phase I/II Study of Arsenic Trioxide/Bortezomib/Ascorbic Acid Combination Therapy for the Treatment of Relapsed or Refractory Multiple Myeloma

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Abstract

Purpose: This multicenter, open-label, phase I/II dose escalation study assessed the safety/tolerability and initial efficacy of arsenic trioxide/bortezomib/ascorbic acid (ABC) combination therapy in patients with relapsed/refractory multiple myeloma.

Experimental Design: Enrolled in six cohorts, patients were given arsenic trioxide (0.125 or 0.250 mg/kg), bortezomib (0.7, 1.0, or 1.3 mg/m^2), and a fixed dose of ascorbic acid (1 g) i.v. on days 1, 4, 8, and 11 of a 21-day cycle for a maximum of eight cycles. The primary end point was safety/tolerability of the ABC regimen.

Results: Twenty-two patients (median age, 63 years) were enrolled, having failed a median of 4 (range, 3-9) prior therapies. One occurrence of grade 4 thrombocytopenia was observed. One patient had asymptomatic arrhythmia and withdrew from the study. Objective responses were observed in 6 (27%) patients, including two partial responses and four minor responses. Median progression-free survival was 5 months (95% confidence interval, 2-9 months), and median overall survival had not been reached. The 12-month progression-free survival and overall survival rates were 34% and 74%, respectively. One (minor response) of six patients receiving the lowest dose of bortezomib (0.7 mg/m^2) and 5 (2 partial responses and 3 minor responses) of 16 patients receiving the higher doses (1.0 or 1.3 mg/m^2) responded.

Conclusions: The ABC regimen was well tolerated by most patients, and it produced preliminary signs of efficacy with an objective response rate of 27% in this heavily pretreated study population. These findings warrant further clinical evaluation of the ABC combination for treatment of relapsed/refractory multiple myeloma.

Multiple myeloma is an incurable cancer that occurs in 3 to 4 per 100,000 people in the United States (1), making it one of the most common primary cancers of the bone marrow. In 2006, it is estimated that more than 16,500 people in the United States will have been diagnosed with multiple myeloma, and deaths from this disease will exceed 11,000 (2). The vast majority of patients with multiple myeloma will relapse or become refractory to treatment, and less than 10% of patients will survive longer than 10 years after diagnosis (3).

Standard of care for relapsed or refractory multiple myeloma currently includes salvage single-agent or combination chemotherapy; thalidomide-, lenalidomide-, or bortezomib-based regimens; or melphalan-based autologous stem cell transplantation (4, 5). These approaches typically achieve response rates of only 10% to 30% and generally last only several months (6, 7). Furthermore, the adverse side effects associated with these salvage regimens may be intolerable to elderly patients. Therefore, a medical need exists for the development of new treatments that are more effective, durable, and tolerable than what is currently available for patients with relapsed or refractory multiple myeloma.

Arsenic trioxide (Trisenox, Cephalon, Inc., Frazer, PA) is a promising antineoplastic chemotherapeutic agent for the treatment of multiple myeloma. In preclinical studies, arsenic trioxide reduced viability, induced apoptosis, and caused growth inhibition in myeloma cell lines at concentrations low enough for safe use in patients (8–10). In early clinical studies of arsenic trioxide for patients with advanced refractory multiple myeloma, this drug produced significant, albeit minor, responses in 21% to 33% of patients with daily dosing schedules (11, 12).

Arsenic trioxide is thought to exert its antitumor effects in part by generating reactive oxygen species (13). The sensitivity of myeloma cell lines to the cytotoxic effects of arsenic trioxide is markedly enhanced by the addition of ascorbic acid, as

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Conflict of interest: J.R. Berenson has a commercial relationship with Cephalon, Inc. and a consultancy with Millenium Pharmaceuticals.

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shown both *in vitro* and in severe combined immunodeficiency (SCID-hu) murine models (14). This synergy is thought to arise through ascorbic acid–mediated depletion of intracellular glutathione, which neutralizes the reactive oxygen species generated by arsenic trioxide. In support of this, a small phase I study in patients with stage III relapsed or refractory multiple myeloma showed that ascorbic acid administration decreased intracellular glutathione and increased sensitivity of patient myeloma cells to arsenic trioxide (15).

Bortezomib (Velcade, Millennium Pharmaceuticals, Inc., Cambridge, MA) is a first-in-class, modified dipeptidyl boronic acid proteasome inhibitor that is currently approved for the treatment of patients with multiple myeloma who have received at least one prior therapy. Proteasome inhibitors exert their antitumor effect primarily by interfering with the ubiquitin-proteasome pathway and disrupting intracellular protein homeostasis, eventually leading to cell cycle blockade, induction of apoptosis, and suppression of angiogenesis (1, 16, 17).

The efficacy and safety of bortezomib at multiple dosages have been studied in two phase II studies [the Study of Uncontrolled Multiple Myeloma Managed with Proteasome Inhibition Therapy (SUMMIT) and the Clinical Response and Efficacy Study of Bortezomib in the Treatment of Relapsing Multiple Myeloma (CREST)] and in one phase III study [the Assessment of Proteasome Inhibition for Extending Remissions (APEX)]. In these studies, patients with relapsed or refractory multiple myeloma received single-agent bortezomib at doses of 1.0 mg/m^2 (CREST only) or 1.3 mg/m^2 (SUMMIT, CREST, and APEX). The objective response rates (ORR), including complete response, partial response, and minor response, were 33% for the lower dose of bortezomib and 35% to 50% for the higher dose (18–20). In all of these studies, the most clinically important adverse effect was peripheral neuropathy. The incidence of grade 3 or 4 peripheral neuropathy for patients receiving bortezomib 1.0 mg/m^2 was 8% (19). By comparison, for patients receiving bortezomib 1.3 mg/m^2, the incidence ranged from 8% to 15% (18–20). Thus, the lower dose of bortezomib exhibits significant antimyeloma activity with reduced toxicity.

Preclinical studies have shown that the combination of arsenic trioxide and bortezomib at low concentrations has synergistic antiproliferative and antimyeloma activity *in vitro* and in xenograft animal models (21), suggesting that a low-dose regimen of arsenic trioxide and bortezomib may have the potential to treat chemoresistant multiple myeloma both effectively and safely. This multicenter, open-label, phase I/II, dose escalation study assessed the safety and tolerability and the initial efficacy of arsenic trioxide/bortezomib/ascorbic acid (ABC) combination therapy for patients with relapsed or refractory multiple myeloma.

Materials and Methods

Study design. This study was a phase I/II open-label, multicenter trial designed to evaluate the safety and tolerability and the initial efficacy of ABC combination therapy among patients with multiple myeloma. Institutional Review Board approval and individual written consent from the patients were obtained before start of the study. Patients with relapsed or refractory multiple myeloma were randomized to one of six treatment arms: arsenic trioxide at 0.125 mg/kg and three escalating doses of bortezomib (0.7, 1.0, and 1.3 mg/m^2) and arsenic trioxide at 0.25 mg/kg and the same three escalating doses of bortezomib (0.7, 1.0, and 1.3 mg/m^2). The bortezomib dose was escalated if patients at the previous dose levels tolerated the treatment without unacceptable dose-limiting toxicities (DLT). Each treatment cycle lasted 3 weeks (21 days) and consisted of four i.v. injections of bortezomib infused over 3 to 5 s, arsenic trioxide infused over 1 to 2 h, and ascorbic acid (1 g i.v.) on days 1, 4, 8, and 11 followed by a 10-day rest period. Patients were eligible to receive a maximum of eight cycles of treatment. The arsenic trioxide dosage and administration schedule used in this study were modeled after those of an earlier study showing that arsenic trioxide (0.25 mg/kg) given twice weekly could produce clinical responses at a rate similar to that produced by daily dosing (22). At least three patients were enrolled into each dose level. Safety data were obtained before more patients were enrolled to the next higher dose level.

Patient selection. Male and female patients ages 18 years or older with measurable disease (defined as a monoclonal immunoglobulin spike on serum electrophoresis of $\geq$1 g/dL or urine monoclonal immunoglobulin spike of $\geq$200 mg/24 h) were enrolled in this study. Before the study began, patients had to have relapsed after a response to standard first-line chemotherapy or be refractory to their most recent chemotherapy and have a life expectancy of >3 months. They had to have had a Karnofsky performance status of $\geq$60, baseline platelet count of $\geq 50 \times 10^9$/L (if the bone marrow was extensively infiltrated, $\geq 30 \times 10^9$/L), hemoglobin of $\geq$8.0 g/dL, and an absolute neutrophil count of $\geq 1.0 \times 10^9$/L. Patients had to be willing to use contraception for the duration of the study, or females had to be postmenopausal or surgically sterilized.

Patients were excluded from the study if they had previous arsenic trioxide plus bortezomib combination therapy; POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes); plasma cell leukemia; major surgery within 4 weeks of the screening visit; active infection (including HIV and hepatitis B or C); New York Hospital Association class III or IV heart failure; severe hypercalcemia (serum calcium $\geq$14 mg/dL or 3.5 mmol/L); chemotherapy within 3 weeks or nitrosoureas within 6 weeks of study enrollment; corticosteroids (>10 mg/d prednisone or equivalent) within 3 weeks of study enrollment; immunotherapy, antibody therapy, or radiation therapy within 4 weeks of study enrollment; uncontrolled hypertension, diabetes mellitus, or other serious medical or psychiatric illness; history of allergies to compounds similar to arsenic trioxide, bortezomib, boron, or mannitol; or >grade 1 neuropathy at baseline. Pregnant and nursing females were also excluded.

Pretreatment assessments. Disease assessments (Karnofsky performance status, complete neurologic examination, skeletal survey, bone marrow aspirate and biopsy, β_2-microglobulin, C-reactive protein, immunofixation, and serum and urine electrophoresis to quantify immunoglobulin) were done within 14 days of day 1 of cycle 1 of treatment. A medical history was obtained, and a complete neurologic and physical examination was done at baseline; a 12-lead electrocardiogram and posteroanterior and lateral chest X-rays were done. A bone marrow aspirate and biopsy were evaluated. Clinical laboratory tests, including hematology, clinical chemistry (blood urea nitrogen, alkaline phosphatase, serum creatinine, uric acid, total bilirubin, lactate dehydrogenase, aspartate transaminase, alanine transaminase), electrolyte (magnesium, potassium, sodium, chloride, calcium) and glucose panel, total protein, amylase, albumin, urinalysis, and serum pregnancy tests for women of childbearing potential, were also done at the screening visit and on day 1 of each cycle.

Safety assessments. On days 1, 4, 8, and 11 of each cycle, patients had complete blood cell counts done. Other procedures repeated at each visit included monitoring for adverse effects, vital signs, review of concomitant medications and support therapies, interval history, neurotoxicity questioning, and physical examination. For each succeeding cycle, magnesium and potassium level determinations and electrocardiogram were repeated on day 8, and body weight, height,

blood chemistry, total serum protein, and serum albumin were measured on day 11.

Toxicities were defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events v.3.0. An unacceptable DLT was defined as a study drug–related event that included any of the following: grade 4 hematologic toxicity, grade 3 thrombocytopenia with grade 3 or 4 hemorrhage, grade 3 or 4 nausea and vomiting refractory to antiemetic therapy, or any other grade ≥3 nonhematologic toxicity.

Patients who showed disease progression after the end of the first cycle were eligible to receive dexamethasone (40 mg orally or i.v.) on days 1, 4, 8, and 11 in addition to ABC combination therapy. Any patient who showed disease progression at the subsequent disease assessment was excluded from the study.

Patients who developed an unacceptable DLT had their study medication stopped. If a DLT was seen in one patient at any dose level during the first cycle, up to three additional patients were recruited to that dose level; if DLT was seen in two patients, no additional patients were recruited to that level, and up to six additional patients were recruited to the next lower dose level. The maximum tolerated dose was defined as the highest dose level at which less than 33% of patients experience unacceptable DLT. Patients with a hematologic DLT had their therapy held, followed by twice-weekly assessment of blood cell counts, and resumed participation in the study only if their DLT normalized within 3 weeks.

Patients who completed eight cycles of ABC therapy were eligible for maintenance therapy, with the same doses given every other week (days 1 and 15) and the maintenance treatment cycle consisting of 28 days. Maintenance therapy was scheduled to continue indefinitely unless patients experienced an unacceptable DLT, developed disease progression, or chose to discontinue treatment. Concomitant medications and supportive therapies were noted. Permitted medications and treatments include granulocyte growth factors (or granulocyte macrophage colony-stimulating factor), thrombopoietin or other platelet growth factors, immunoglobulin infusions, blood products, erythropoietin, plasmapheresis, and bisphosphonates.

Response criteria. Patient responses to treatment were monitored on day 1 of each cycle, at the end of the study, and on day 1 of each cycle of maintenance therapy. Responses were evaluated according to criteria developed by Blade et al. (23). A complete response was defined as a negative immunofixation test for the original monoclonal protein (M-protein) from blood and urine, <5% plasma cells in bone marrow on at least two determinations 6 weeks apart, no increase in the size or number of lytic bone lesions, and the disappearance of soft tissue plasmacytomas for at least 6 weeks. A partial response was defined as ≥50% reduction in serum M-protein, ≥50% reduction in the size of soft tissue plasmacytomas for at least two determinations 6 weeks apart, ≥90% reduction in 24-h urinary light chain excretion or levels <200 mg, and no increase in size or number of lytic bone lesions. A minor response was defined as a 25% to 49% reduction in serum M-protein and the size of plasmacytomas, a 50% to 89% reduction in 24-h light-chain excretion (although still >200 mg/24 h) for at least two determinations 6 weeks apart, and no increase in the size or number of lytic bone lesions. Progressive disease was defined as one or more of the following: >25% increase in serum M-protein (confirmed absolute increase of ≥5 g/L), >25% increase in 24-h urinary light-chain excretion (confirmed absolute increase of ≥200 mg/24 h), >25% increase in plasma cells in a bone marrow aspirate or on trephine biopsy (absolute increase of at least 10%), an increase in the size of lytic bone lesions or soft tissue plasmacytomas, development of new bone lesions or plasmacytomas, or development of hypercalcemia.

Table 1. Patient demographics (N = 22)

Median age (range), y	63 (43-76)
Median number (range) of failed therapies	4 (3-9)
No. patients by failed therapies	
Arsenic trioxide	2
Melphalan	6
Thalidomide/lenalidomide	4
Bortezomib	5
Peripheral stem cell transplant	2
Serum M-protein (g/dL)	
Mean (range)	3.8 (0.7-10.3)
Urine M-protein (g/24 h)	
Mean (range)	2.1 (0-18.3)
β_2-Microglobulin	
Mean (range)	5.1 (1.6-19.5)

Table 2. Adverse events (N = 22)

Adverse event*	No. patients	Cohort
Thrombocytopenia (grade 4)	1	6
Pneumonia	2	1, 6
Chest pain	1	1
Abdominal pain	1	6
Back pain	1	4
Increased QT†	1	3
Asymptomatic arrhythmia	1	3
Cardiomyopathy	1	2
Bacteremia	1	6
Bortezomib intolerance	1	6
Hyperkalemia	1	4
Severe decrease in quality of life‡	1	3

*All adverse events were grade 1 or 2, unless otherwise noted.
†This patient had elevated QT at baseline.
‡As judged by the study investigators.

Statistical analysis. The primary statistical end point of this study was the safety and tolerability of ABC combination therapy, as reflected in the maximum tolerated dose and DLT, for patients with relapsed or refractory multiple myeloma. Characterization of these safety variables as well as disease characteristics and baseline patient characteristics was done by using descriptive statistics. Secondary statistical end points include the proportion of patients responding to therapy (complete response, partial response, and minor response), time to progression of disease, progression-free survival, and overall survival.

Results

Patient disposition. A total of 22 patients (median age, 63 years) were enrolled in the study. The patients had a median of 4 (range, 3-9) prior failed therapies. Two patients had previously received arsenic trioxide therapy; five patients had bortezomib treatment; six patients had melphalan; four patients had thalidomide/lenalidomide; and two patients underwent peripheral stem cell transplantation. Patient demographics are summarized in Table 1. Three to six patients were enrolled in each of the six treatment cohorts. The median number of treatment cycles completed was three cycles (range, 0-8). To date, all patients have either completed the study or are off the study for reasons of adverse effects, patient choice, or progressive disease. One patient went on maintenance therapy after completing eight therapy cycles. During the study, one patient died of a ruptured diverticulum considered unrelated to the study treatment. Following the study, five other patients died of disease-related complications.

Safety and tolerability. The ABC combination therapy was well tolerated by most patients. The adverse effects and their

Table 3. Patient responses to ABC therapy (N = 22)

Objective responses	*n* (%)
Overall response	6 (27)
CR	0 (0)
PR	2 (9)
MR	4 (18)
Disease control (CR + PR + MR + SD)	15 (68)
Objective responses by failed prior therapies, *n* (%)	
Arsenic trioxide	0 (0)
Melphalan	1 (17)
Thalidomide/lenalidomide	1 (25)
Bortezomib	0 (0)
Peripheral stem cell transplant	1 (50)
Kaplan-Meier survival estimates (mo)	
Median progression-free survival (95% CI)	5 (2-9)
Median overall survival	Not reached
12-mo survival rates, %	
Progression-free survival (95% CI)	34 (13-55)
Overall survival (95% CI)	74 (55-94)

Abbreviations: CR, complete response; PR, partial response; MR, minor response; SD, stable disease; 95% CI, 95% confidence interval.

frequencies are listed in Table 2. One occurrence of grade 4 hematologic adverse effect (i.e., thrombocytopenia) was observed. One patient who showed prolonged QTc interval at baseline experienced an increase in QTc interval (495 msec) and asymptomatic premature ventricular complexes during the first week of the first treatment cycle. Consequently, the patient was withdrawn from the study. All other adverse effects were grade 1 or 2. Treatment-related peripheral neuropathy was not observed in any patients in this study.

Efficacy. All 22 patients were evaluated for efficacy to ABC therapy without the addition of dexamethasone. (Per protocol, no patients met the criteria to require the addition of dexamethasone to the study treatment.) Patient responses are summarized in Table 3. Clinical responses were observed in six patients (two partial responses and four minor responses), for an ORR of 27%. Of the 16 patients who showed no clinical response, nine had stable disease, for a disease control rate (complete response + partial response + minor response + stable disease) of 68%. The remaining patients had progressive disease (n = 6) or had failed to complete one full treatment cycle (n = 1). Based on Kaplan-Meier estimates of survival, median progression-free survival was 5 months (95% confidence interval, 2-9 months; Fig. 1). The median overall survival has not been reached yet with a median follow-up of 13 months (range, 7-20 months; Fig. 2). The progression-free survival and overall survival rates at 12 months after the start of treatment were 34% and 74%, respectively.

Of the six patients receiving the lowest dose of bortezomib (0.7 mg/m^2), one showed a clinical response (one minor response; 17%), whereas 5 of 16 patients receiving the two higher bortezomib doses responded (two partial responses and three minor responses; 31% total; Table 4).

Discussion

The vast majority of patients with multiple myeloma develop resistance to chemotherapy, which is believed to arise from acquired resistance to apoptosis, allowing tumors to withstand high levels of chemotherapy. Increased activity of nuclear factor-κB is associated with increased resistance and tumor cell survival in multiple myeloma (24, 25). In addition, up-regulation of antiapoptotic genes (e.g., *Bcl-2*, *Bcl-x$_L$*, and *Mcl-1*; refs. 26–28), increased expression of P-glycoprotein product of the *mdr1* gene (29), and enhanced drug metabolism via the glutathione redox pathway (30, 31) have also been reported as mechanisms of chemoresistance in multiple myeloma.

Bortezomib and arsenic trioxide are antineoplastic agents capable of overcoming adaptive cellular changes in chemorefractory multiple myeloma. Both bortezomib and arsenic trioxide suppress nuclear factor-κB activity by inhibiting IκB degradation (32, 33), although by distinct mechanisms, and can functionally modulate diverse signaling pathways, such as those involving mitogen-activated protein kinase and

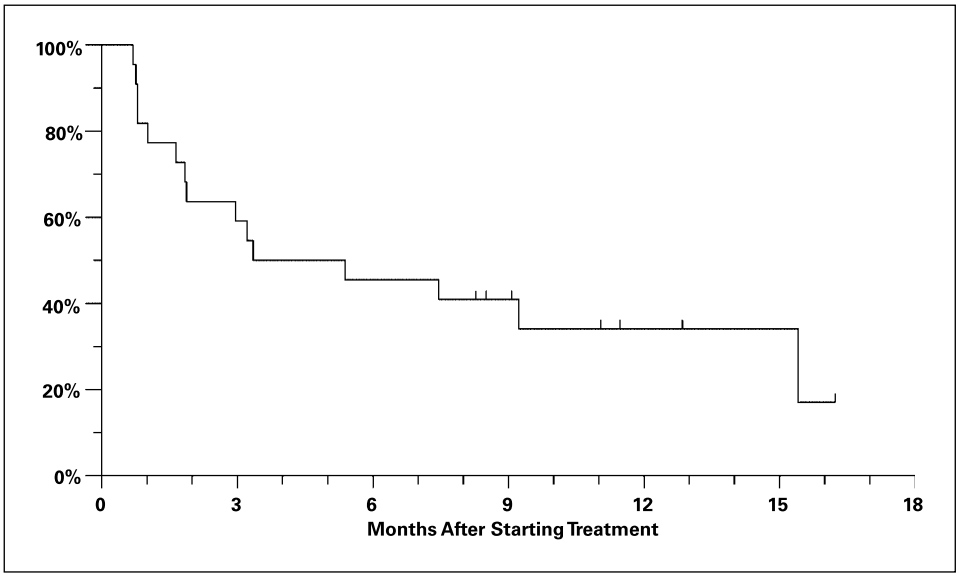

Fig. 1. Kaplan-Meier estimates of progression-free survival among patients who received ABC therapy (N = 22).

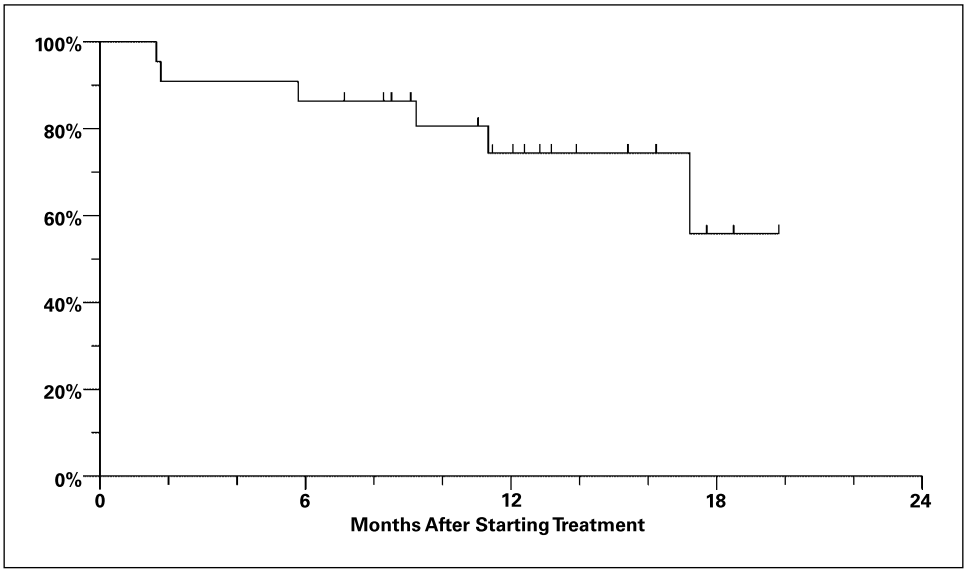

Fig. 2. Kaplan-Meier estimates of overall survival among patients who received ABC therapy (N = 22).

phosphatidylinositol 3-kinase/Akt (32, 34). Additionally, both agents promote mitochondrial cytochrome *c* release, which in turn activates caspase-mediated apoptosis (32, 35). Furthermore, arsenic trioxide is insensitive to drug-efflux pump mechanisms and is capable of overcoming prosurvival cytokines, interleukin-6, and BCL-x_L in chemorefractory multiple myeloma (36), and bortezomib inhibits DNA repair machinery and suppresses adhesion of multiple myeloma cells to bone marrow stromal cells (37, 38). Therefore, the synergistic cytotoxic effects observed with the ABC combination in both *in vitro* and *in vivo* preclinical studies (21) are likely attributable to the overlapping and distinct mechanisms of action of arsenic trioxide and bortezomib (39). Furthermore, the cytotoxicity of arsenic trioxide may be enhanced by ascorbic acid–mediated glutathione depletion (36); however, some preclinical *in vitro* research disputes this point. In a recent study, ascorbic acid was shown to protect leukemia and multiple myeloma cell lines from arsenic trioxide toxicity by reducing intracellular reactive oxygen species (40). In addition, a separate report described ascorbic acid as suppressing bortezomib-mediated inhibition of proteasome activity and abrogated the cell killing by this drug *in vitro* (41). These paradoxical effects of ascorbic acid have been associated with intracellular ascorbic acid concentration and with the timing of when these agents are given in relation to each other.

The ABC combination regimen was well tolerated in this study. In particular, treatment-emergent peripheral neuropathy was not observed. Previous studies of single-agent bortezomib have shown a significant occurrence of grade 3 or 4 peripheral neuropathy. Notably, whereas 5 of 54 (9%) of patients in the CREST study discontinued because of peripheral neuropathy, none of the patients in this ABC study discontinued because of treatment-related neuropathy. Thus, the ABC combination was not associated with the emergence of treatment-related peripheral neuropathy in this study.

A grade 4 thrombocytopenia was observed in a patient receiving the highest dose of bortezomib but not among patients receiving the lower doses. By comparison, patients treated with bortezomib 1.3 mg/m^2 in the CREST, SUMMIT, and APEX studies experienced grade 3 or 4 thrombocytopenia at a rate of 23%, 31%, and 30%, respectively (18–20).

Earlier clinical studies of arsenic trioxide in patients with acute promyelocytic leukemia have reported some prolongation of the QTc interval in 38% to 93% of patients (42–44). Other groups have reported complete atrioventricular block and torsades de pointes and sudden death associated with arsenic trioxide use in patients with acute promyelocytic leukemia (45, 46). In this study of ABC, only 1 patient (5%) with a long QTc at baseline was removed from the study because of asymptomatic premature ventricular complexes.

Table 4. Patient responses by cohort (N = 22)

Cohort	Arsenic trioxide dose (mg/kg)	Bortezomib dose (mg/m^2)	No. patients enrolled	Best responses
1	0.125	0.7	3	1 MR, 2 PD
2	0.125	1.0	3	1 PR, 1 SD, 1 PD
3	0.125	1.3	4*	1 PR, 2 PD
4	0.25	0.7	3	2 SD, 1 PD
5	0.25	1.0	3	3 MR
6	0.25	1.3	6	6 SD

Abbreviations: CR, complete response; PR, partial response; MR, minor response; SD, stable disease.
*One patient did not complete one full cycle of therapy.

Thus, the addition of bortezomib and ascorbic acid to arsenic trioxide in the ABC regimen does not seem to increase the risk of cardiotoxicity associated with daily arsenic trioxide usage in acute promyelocytic leukemia. A similarly low incidence of cardiac events was reported in another study in which arsenic trioxide was given at 0.1 to 0.25 mg/kg twice weekly for 11 weeks (47).

We have shown activity of the ABC combination therapy (ORR, 27%) in difficult-to-treat patients with multiple myeloma refractory to multiple chemotherapies, including arsenic trioxide–, bortezomib-, thalidomide/lenalidomide–, and melphalan-based regimens. Making limited comparisons between the ABC regimen and single-agent arsenic trioxide or bortezomib or other arsenic trioxide or bortezomib combinations may provide some insight into the relative activities of arsenic trioxide–containing regimens. Two separate phase II studies of single-agent arsenic trioxide (0.15-0.25 mg/kg) in heavily pretreated refractory multiple myeloma resulted in objective responses in 21% to 33% of patients (11, 12). The ORRs reported in arsenic trioxide combination studies were 48% in a study of melphalan (0.1 mg/kg), arsenic trioxide (0.25 mg/kg), and ascorbic acid (1 g) combination therapy and 25% in a study of arsenic trioxide (0.25 mg/kg), ascorbic acid (1 g), and dexamethasone (20 mg; refs. 48, 49). In the phase II and III studies of single-agent bortezomib, the ORR among patients who received bortezomib at 1.0 mg/m^2 (n = 27) was 33%, and the ORR among patients who received bortezomib at 1.3 mg/m^2 was 35% to 50% (18–20). In combination studies of bortezomib, the ORRs reported were 68% in a study of bortezomib (1.0 mg/m^2) and melphalan (0.10 mg/kg) and 73% in a study of bortezomib (0.9-1.5 mg/m^2) and pegylated liposomal doxorubicin (Doxil, Ortho Biotech Products LP, Bridgewater, NJ; 30 mg/m^2; refs. 50, 51). Taken together, these limited comparisons suggest that the activity of the ABC combination in patients with relapsed or refractory multiple myeloma may be less robust than that of combination regimens of chemotherapy and either one of these agents. The 27% response rate observed in this study may reflect an inhibitory effect of ascorbic acid on the clinical activity of the arsenic trioxide/bortezomib combination, as has been observed in some preclinical studies (41). Therefore, larger phase II studies of ABC therapy will need to be done to establish whether in fact ascorbic acid has any potential deleterious effects on these agents in the clinical setting.

The results of this ABC study are encouraging, particularly considering the advanced median age of the study population and the numerous prior therapies from which these patients had relapsed. Further investigations on a more expanded scale are warranted to establish more fully the safety and efficacy of the ABC combination. The ABC regimen may offer an active, yet tolerable, therapeutic option for older patients with relapsed or refractory multiple myeloma who are unable to endure other chemotherapy or steroid-based regimens. In addition, the combination of melphalan, arsenic, and bortezomib may be worthwhile to evaluate given the promising results of this ABC study and those of other phase I and II trials showing that melphalan/arsenic trioxide and melphalan/bortezomib combination treatment are also well tolerated and have significant clinical activity (48, 50).

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