

Bortezomib, Ascorbic Acid and Melphalan (BAM) Therapy for Patients with Newly Diagnosed Multiple Myeloma: An Effective and Well-Tolerated Frontline Regimen

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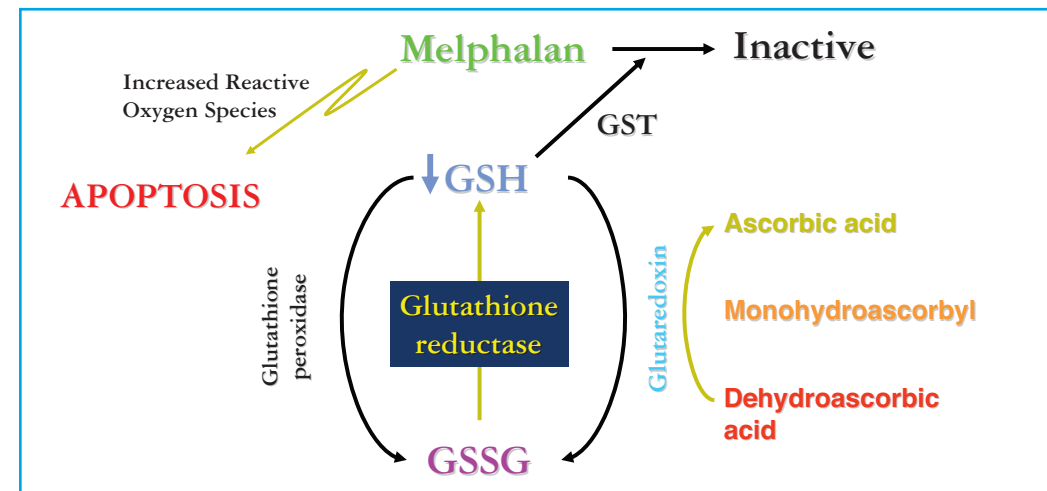
INTRODUCTION

It has been shown that combinations of treatment for cancer patients are more efficacious than single agent therapy in many cases. Of relevance has been the *in vitro* studies conducted in the Berenson laboratory that have demonstrated significant synergy between bortezomib and melphalan in treating myeloma cells. The sensitivities to various cytotoxic agents of chemoresistant myeloma cells were increased 10,000 to 100,000-fold when the cells were treated with 5 ng/ml of bortezomib together with melphalan, indicating that much lower doses of each drug (bortezomib and melphalan) are probably required in treating myeloma patients in this combination regimen compared to when these agents are used alone.

In light of the highly effective combination observed when bortezomib was combined with melphalan in our preclinical studies, we conducted a phase I/II trial in relapsed or refractory multiple myeloma using bortezomib 0.7 mg/m² (less than half of the dose used in the current study) escalated to 1.0 mg/m² on days 1, 4, 8 and 11 every 4 weeks in combination with doses of oral melphalan from 0.025 mg/kg escalated up to 0.25 mg/kg daily on days 1-4. Dose-limiting toxicity occurred among patients receiving bortezomib 1.0 mg/m² with the highest dose of melphalan (0.25 mg/kg) and led to the assignment of bortezomib 1.0 mg/m² and melphalan 0.10 mg/kg as the maximum-tolerated dose. A high response rate (68%) was observed and, in turn, provided the rationale for this clinical trial.

The addition of ascorbic acid (AA) or vitamin C to the regimen was based on prooxidant properties of this vitamin in addition to its better known antioxidant actions. In the plasma, AA is oxidized to dehydroascorbic acid (DHA) before being transported into the cell, where AA is regenerated through a reaction which converts intracellular free glutathione (GSH) to GSH disulfide. This reaction depletes intracellular GSH, the molecule that eliminates reactive oxygen species (ROS), thereby increasing hydrogen peroxide production and sensitizing MM cells to alkylating agents. Elevated intracellular levels of GSH and GSH-related enzymes in MM cells have been shown to confer drug resistance to alkylating agents such as melphalan. Thus, the combination of bortezomib, ascorbic acid and melphalan (BAM) may overcome resistance to melphalan in MM cells, which provided the rationale for evaluating BAM in MM patients.

Melphalan, Gultathione and Ascorbic Acid



ENDPOINTS

- Primary endpoints:
 - To determine the overall response rate [(the combined complete response (CR) + near CR (nCR) + very good partial response (VGPR) + partial response (PR) + minimal response (MR)] and time to progression of disease.
 - To assess the safety and tolerability of BAM therapy for patients with MM as assessed by the NCI CTCAE version 3.0.
- Secondary endpoints:
 - To assess the progression-free survival and overall survival;
 - To assess time to disease progression among subjects who continue on maintenance treatment with bortezomib.

INCLUSION/EXCLUSION CRITERIA

- Inclusion criteria
 - Male or female patients ≥18 years of age (hospitalized patients are eligible)
 - Symptomatic, previously untreated multiple myeloma
 - Karnofsky performance status ≥60
 - Life-expectancy >3 months
- Exclusion criteria
 - POEMS syndrome
 - Plasma cell leukemia
 - Active infection, known HIV infection, or known active hepatitis B or C viral infection
 - Female subject is pregnant or breast-feeding
 - ≥Grade 2 peripheral neuropathy within 14 days before enrollment

TREATMENT SCHEMA

- This is a single-arm phase II study that evaluated the combination of bortezomib, oral AA and low-dose oral melphalan (BAM) for 35 newly diagnosed patients with symptomatic myeloma.
- Treatment consisted of a 28-day cycle for a maximum of 8 cycles.
 - Bortezomib was administered in the morning at a dose of 1.0 mg/m² on days 1, 4, 8, and 11 followed by a 17 day rest period.
 - Oral ascorbic acid at a dose of 1g and oral melphalan at 0.1 mg/kg were both administered in the evening on days 1-4 of each cycle.
- Based on preclinical studies suggesting potential inhibitory effects of AA on bortezomib's anti-myeloma activity, bortezomib was administered in the morning and AA with melphalan in the evening.
- Patients who were treated to maximum response plus two additional cycles or after completion of eight cycles of therapy and without disease progression were subsequently treated with bortezomib at a dose of 1.3 mg/m² every other week until progressive disease occurred.

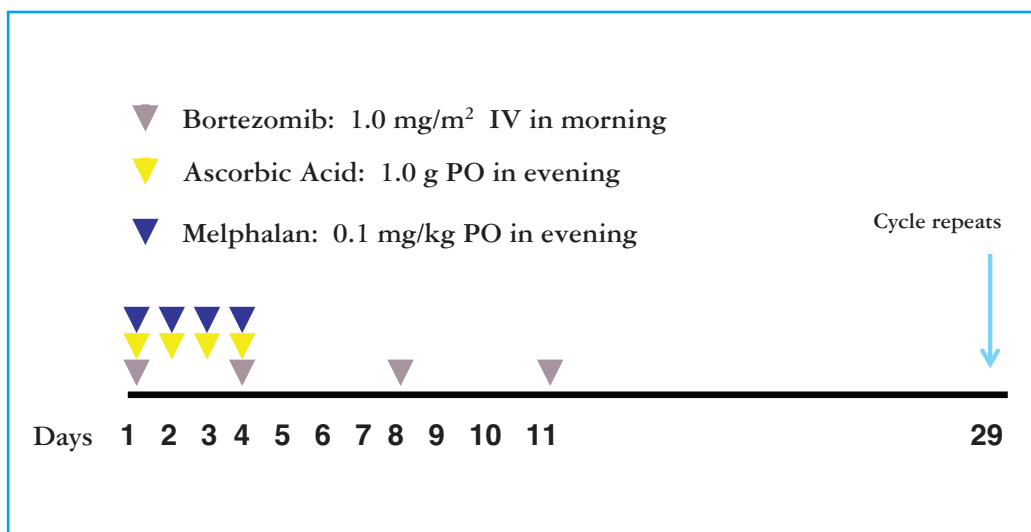


Table 1. Patient Demographics

Patient Demographics (N=35)	
Median Age (years)	70 (range: 50-90)
Male: Female	20:15
ISS Stage	
I	6
II	17
III	11
Unknown	1
Serum M-protein (g/dl)	
Median	2.70
Range	0.10 - 5.89
Urine M-protein (mg/24h)	
Median	110
Range	0.0 - 14,963
Serum Creatinine (mg/dL)	
Median	1.0
Range	0.4 - 3.5
Evaluable for Efficacy	31
Too early to assess	0
Not evaluable*	4

*1 had nonregimen-related renal failure during cycle 1; 2 had a previous cancer, 1 expired early in cycle 1

Table 2. Patient Responses

Patient Responses (N=31)	
Complete Response (CR) (no serum M-protein)	5* (16%)
Very Good Partial Responses (VGPR) (≥75% decrease in serum M-protein)	3 (10%)
Partial Response (PR) (50-74% decrease in serum M-protein)	4 ^a (13%)
Minor Response (MR) (25-49% decrease in serum M-protein)	11 (35%)
Objective Response (CR+VGPR+PR+MR)	23 (74%)
Stable Disease (SD) (change in M-protein ± 25%)	6 (19%)
Disease Control (CR+VGPR+PR+MR+SD)	29 (94%)
Progressive Disease (PD) (>25% increase in M-protein)	2 (6%)

*1 CR not confirmed by bone marrow
*1 PR not confirmed due to death of patient

RESULTS

Table 3. Patient Status

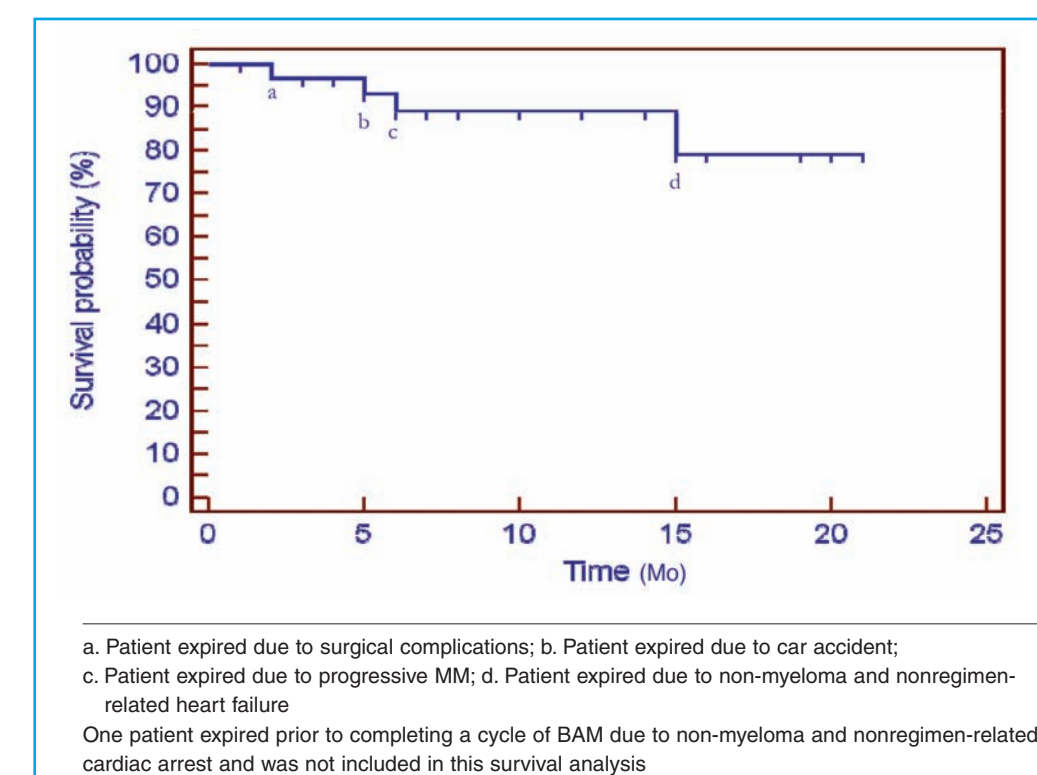
Patient Status (N=35)	
Active on BAM	8
Maintenance Phase (Bortezomib qow)	6
Expired	5*
Off-Study	
Progressive Disease on Study	2
Progressive Disease on Maintenance	5
Adverse Event	4
Non-Evaluable due to Prior Cancer	2
Patient Withdrew	2
Patient had Non-Regimen Related Renal Failure	1
TOTAL	16

*Four deaths were non-myeloma and non-regimen related. One was due to progressive MM.

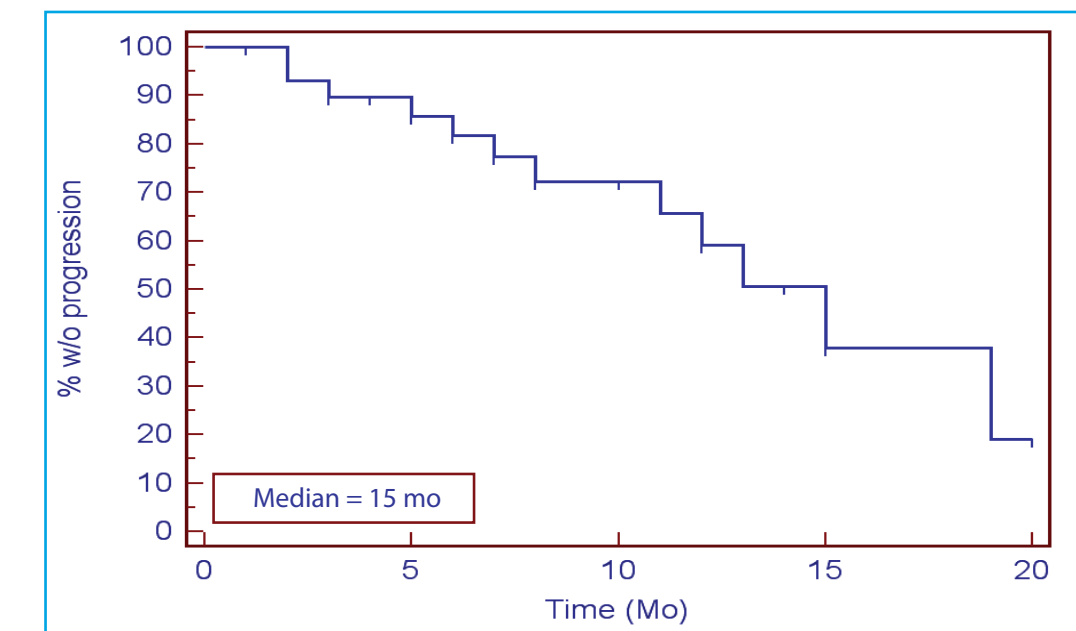
Table 4. Patient Survival

Patient Survival (N=31)	
Remaining on Trial	8
Completed Trial w/Nonprogressive Disease	10
Progressive Disease	9
Time to Progression (Months)	
Median	15
Range	1-20+
Overall Survival (Months)	
Median	N/A
Range	1-21+

Overall Survival



Time to Progression



ADVERSE EVENTS

All patients were evaluable for safety:

- 17 (49%) patients experienced grade 3 or greater side effects
 - The grade 3 side effects included: 3 neutropenia, 2 neuropathy, 2 thrombocytopenia, 2* back pain, 2* weakness, 1 diarrhea, 1 anemia, 1 constipation, 1* hypoalbuminemia, 1* anorexia, 1* worsening congestive heart failure, 1* dehydration, 1* pneumonia, 1* generalized pain, 1* renal failure, 1* hypoglycemia
 - The grade 4 side effects included: 1 thrombocytopenia, 1* cardiac arrest, 1* hip fracture, 1* intractable heart failure, 1* worsening shortness of breath
 - 14 (40%) patients had treatment-emergent neuropathy
 - 10 Grade 1
 - 2 Grade 2
 - 2 Grade 3 (one of those started as a Grade I)
 - Treatment-emergent neuropathy was reversible in all but one case
- *Judged to be not related to study medications

SUMMARY

Bortezomib, Ascorbic Acid and Melphalan (BAM) for Patients with Newly Diagnosed Multiple Myeloma:

- An IMiD- and steroid-free regimen with an excellent response rate (Overall - 74%: 16% CR, 10% VGPR, 13% PR and 35% MR) as frontline therapy
- Well-tolerated with few significant AE's reported
- AE's were predictable and manageable
- Infrequently resulted in ≥Grade 2 neuropathy and most cases of peripheral neuropathy resolved