

A phase II trial of bortezomib + ascorbic acid + melphalan (BAM) combination therapy for patients with newly diagnosed multiple myeloma

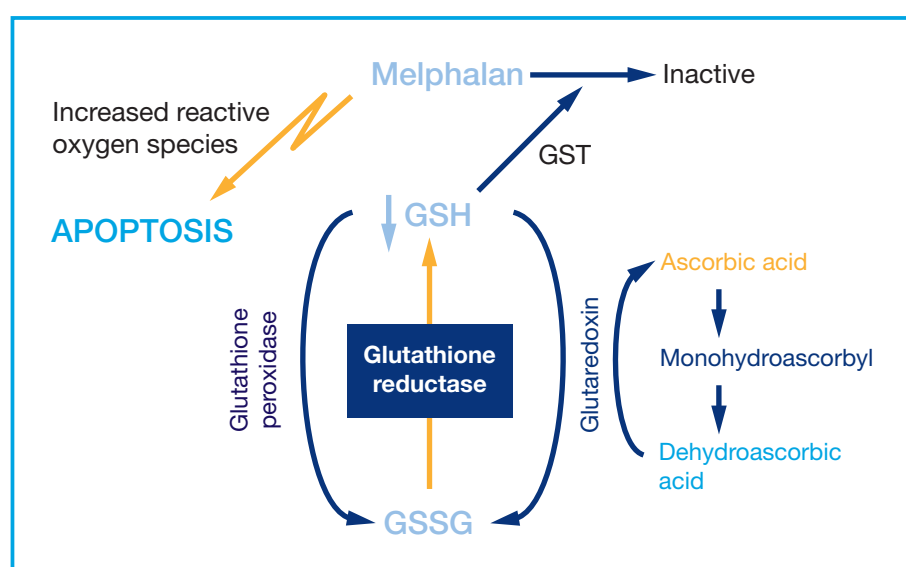
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INTRODUCTION

- It has been shown that combinations of treatment for cancer patients are more efficacious than single-agent therapy in many cases.¹⁻³
- Of relevance have been the *in vitro* studies conducted in the Berenson laboratory that have demonstrated significant synergy between bortezomib and melphalan in treating myeloma cells.⁴
- The sensitivities to various cytotoxic agents of chemoresistant myeloma cells were increased 10,000- to 100,000-fold when the cells were treated with 5ng/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 with 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 0.7mg/m² (less than half of the dose used in the current study) escalated to 1.0mg/m² twice weekly for 2 consecutive weeks every 4 weeks
 - In combination with doses of oral melphalan from 0.025mg/kg escalated up to 0.25mg/kg once daily for 4 days a week every 4 weeks.
- High response rates were observed and, in turn provided the rationale for this clinical trial.⁵
- The addition of ascorbic acid (AA), or vitamin C, to the regimen was based on the fact that it possesses prooxidant properties in conjunction 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 (Figure 1).⁶
- This reaction depletes intracellular GSH, the molecule that eliminates reactive oxygen species (ROS), thereby increasing hydrogen peroxide production and sensitizing MM cells to chemotherapeutic agents.⁷
- 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.⁷⁻⁹
 - Thus, the combination of melphalan, bortezomib and vitamin C (BAM) may overcome resistance to melphalan in MM cells, which provides the further rationale for evaluating BAM in multiple myeloma.

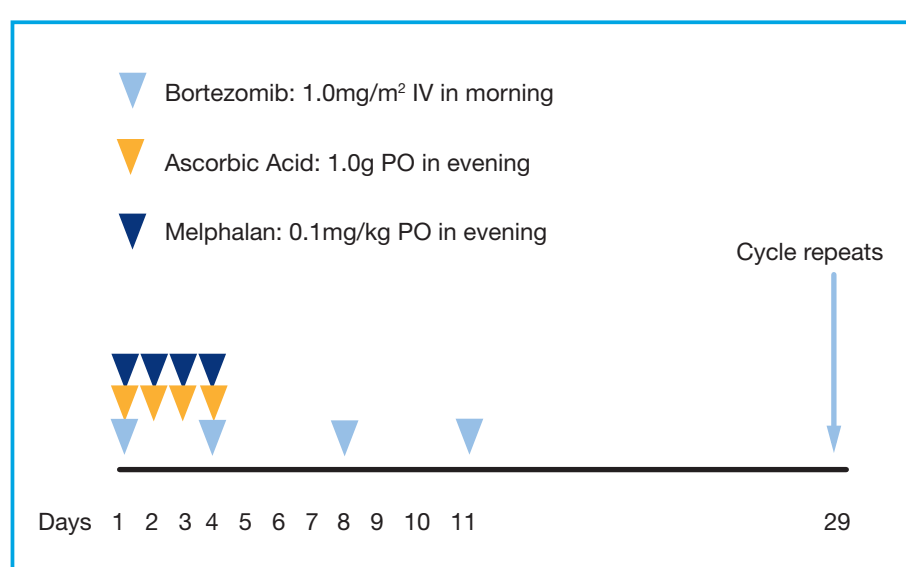
Figure 1. Melphalan, glutathione and ascorbic acid



TREATMENT SCHEMA

- This is a single-arm phase II study that evaluated the combination of bortezomib, oral ascorbic acid and low-dose oral melphalan (BAM) for 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 1.0mg/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 0.1mg/kg were both administered in the evening on days 1-4 of each cycle.
- Patients who were treated to maximum response plus 2 additional cycles or after completion of 8 cycles of therapy and without disease progression were subsequently treated with bortezomib at a dose of 1.3mg/m² every other week until progressive disease occurred.

Figure 2. Treatment schema



RESULTS

Table 1. Patient demographics (N=30)

Median age, years (range)	70 (50-90)
Male:female, n:n	18:12
ISS stage, n	
I	6
II	15
III	8
Unknown	1
Serum M-protein, g/dL	
Median	2.50
Range	0.10-5.26
Urine M-protein, mg/24h	
Median	200
Range	3-14,963
Serum creatinine, mg/dL	
Median	1.1
Range	0.6-3.4
Evaluable for efficacy, n	25
Too early to assess	1
Not evaluable*	4

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

Table 2. Patient responses (N=25)

Response	n (%)
Complete Response (CR) (no serum M-protein)	4* (16)
Very Good Partial Responses (VGPR) (≥ 75% decrease in serum M-protein)	1 (4)
Partial Response (PR) (50-74% decrease in serum M-protein)	5† (20)
Minor Response (MR) (25-49% decrease in serum M-protein)	6 (24)
Objective Response (CR+VGPR+PR+MR)	16 (64)
Stable Disease (SD) (change in M-protein ±25%)	7 (28)
Disease Control (CR+VGPR+PR+MR+SD)	23 (92)
Progressive Disease (PD) (>25% increase in M-protein)	2 (8)

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

Table 3. Patient status (N=30)

Status	n
Active on BAM	8
Maintenance phase (bortezomib qow)	6
Expired	4*
Off-Study	
Progressive disease on study	3
Progressive disease on maintenance	2
Adverse event	3
Non-evaluable due to prior cancer	2
Patient withdrew	1
Patient had non-regimen-related renal failure	1
TOTAL	12

*All deaths were non-myeloma- and non-regimen-related

Table 4. Patient survival (N=25)

Remaining on trial, n	7
Completed trial with non-progressive disease, n	12
Progressive disease, n	6
Time to progression, months	
Median	13+
Range	2-13+
Overall survival, months	
Median	N/A
Range	2-16+

Figure 3. Overall survival

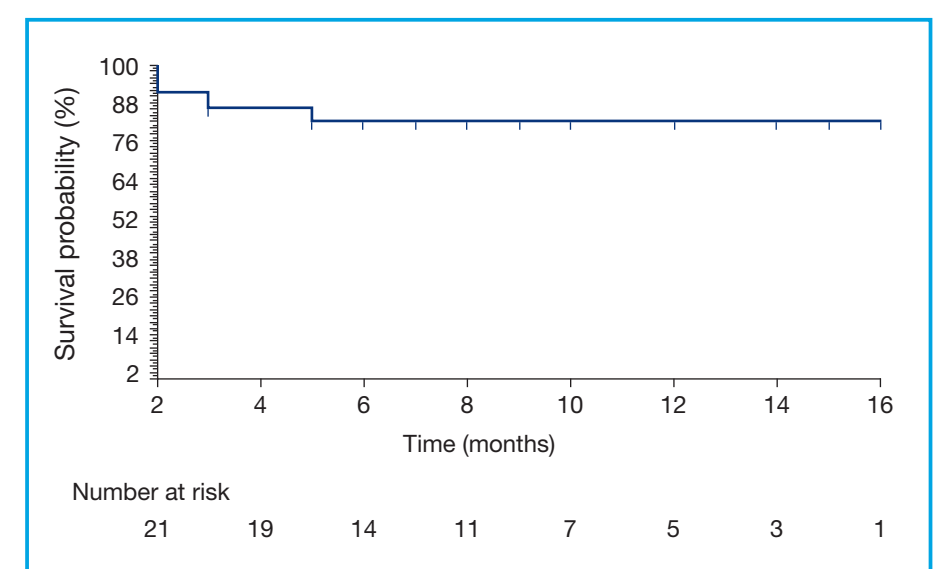
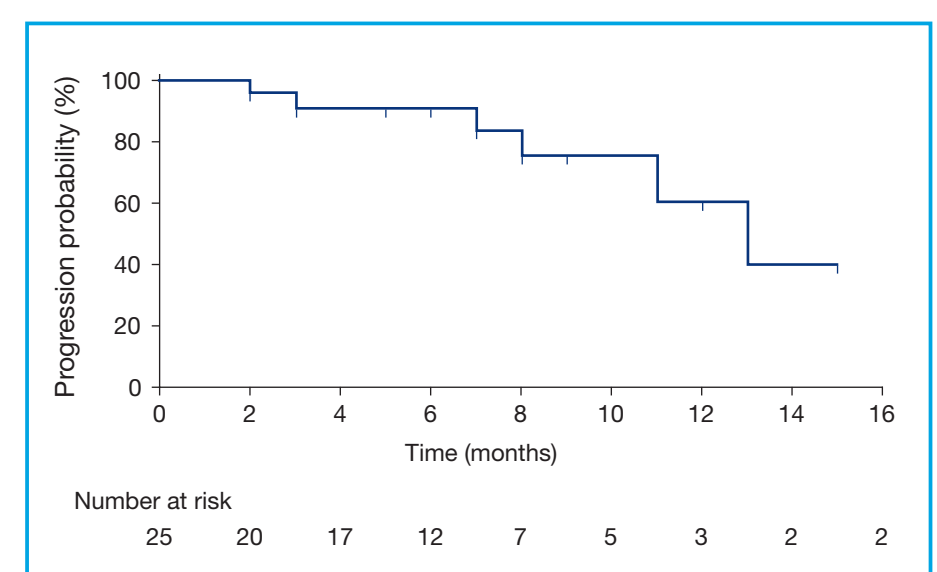


Figure 4. Time to progression



Adverse events

- All patients were evaluable for safety.
- 10 patients experienced grade ≥3 side effects
 - Grade 3 side effects included:
 - 4 neutropenia, 2 neuropathy, 2 thrombocytopenia, 1* worsening congestive heart failure, 1* hypercalcemia, 1* pneumonia, 1 hematologic toxicity, 1* constipation, 1* back pain (*judged to be not related to study medications)
 - Grade 4 side effects included: 1 worsening shortness of breath (judged to be not related to study medications).
- 11 patients had some form of increased neuropathy from baseline
 - 7 grade 1
 - 2 grade 2
 - 2 grade 3 (one of those started as a grade 1).

SUMMARY

- BAM:
 - is a steroid-free regimen with an excellent response rate (64%) as a frontline therapy
 - regimen has been well tolerated with few significant AEs reported
 - infrequently results in grade ≥2 neuropathy.

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