A Phase I/II Study of Oral Melphalan Combined with Panobinostat for Patients with Relapsed or Refractory Multiple Myeloma (MM)

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INTRODUCTION

We and others have shown that panobinostat, a potent histone deacetylase inhibitor (HDACi), significantly inhibits the growth of MM cells *in vitro* and enhances the cytotoxicity triggered by chemotherapeutic agents. Using our SCID-hu models of MM, we have also shown a striking inhibition of MM cell growth *in vivo* when panobinostat was combined with low doses of melphalan compared to treatment with either drug alone. Thus, these preclinical studies provided the rationale for evaluating the combination of oral melphalan with oral panobinostat for the treatment of MM patients with relapsed or refractory disease. We present the results of an ongoing phase I/II, open-label, multicenter, dose-escalation study.

OBJECTIVES

The primary objectives of this study are to:

- Establish the maximum tolerated dose (MTD) and determine the dose-limiting toxicities (DLT) of the combination of panobinostat and melphalan for patients with relapsed or refractory multiple myeloma
- Determine the dose of panobinostat and melphalan to be used in the Phase II portion of the study

The secondary objective of this study is to:

- Determine the efficacy as evidenced by the response rate [combined complete response (CR) + very good partial response (VGPR) + partial response (PR) + minimal response (MR)] of the combination of panobinostat and melphalan for patients with relapsed or refractory multiple myeloma

STUDY DESIGN

This is a phase I/II, open-label, multicenter, dose-escalation study designed to evaluate the efficacy and safety of oral panobinostat given in combination with oral melphalan to patients with relapsed /refractory multiple myeloma. Patients can receive a maximum of eight treatment cycles in this study or are treated to maximum response plus two cycles.

Inclusion criteria

- Male or female patients ≥18 years of age
- Relapsed/refractory MM with measurable disease
- ECOG performance status ≤ 2
- Life-expectancy >3 months

Exclusion criteria

- Impaired cardiac function or clinically significant cardiac diseases
- Screening ECG with a QTc > 450 msec
- Screening echocardiogram or MUGA evidence of LVEF below institutional normal
- POEMS syndrome
- Plasma cell leukemia
- Patients with a prior malignancy within the last 5 years (except for basal or squamous cell carcinoma, or *in situ* cancer of the cervix)
- 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
- Patients who have undergone major surgery
- Severe hypercalcemia
- Patients using medications that have a relative risk of prolonging the QT interval or inducing torsades de pointes

COHORTS & TREATMENT SCHEMAS

The initial treatment schedule involved administering patients oral panobinostat every Monday, Wednesday and Friday (MWF) combined with oral melphalan daily on days 1-5 of a 28-day cycle. Three subjects were enrolled into the first cohort (oral panobinostat 10 mg; melphalan 0.05 mg/kg) and all experienced significant hematological adverse events. During cycle 1, two of three subjects had grade 3 thrombocytopenia and all three patients developed grade 3 neutropenia.

As a result, the melphalan dosing schedule was changed to days 1, 3 and 5. Three subjects were enrolled into this modified first cohort using the same doses (oral panobinostat 10 mg; melphalan 0.05 mg/kg). One subject in this cohort experienced both a grade 3 neutropenia and thrombocytopenia. However, there were no dose-limiting toxicities (DLT) in this cohort and so enrollment into the next cohort (panobinostat at 20 mg and melphalan at 0.05 mg/kg) was initiated.

In this cohort, one subject experienced a DLT (grade 4 thrombocytopenia) while the other two developed grade 3 thrombocytopenia. As a result, 3 additional patients were evaluated at this dose level, but had to be taken off study due to persistent grade 3 neutropenia. Based on the ongoing significant fatigue (grade 1 and 2) among patients treated with LBH89 throughout the treatment cycle, the protocol was revised so that the HDACi was administered only during the first two weeks (days 1, 3, 5, 8, 10, and 12) of the 28-day schedule.

Seven subjects were enrolled into the first cohort using this altered schedule (panobinostat at 20 mg and melphalan at 0.05 mg/kg). One of the first three subjects in this new cohort experienced progressive disease before completing the first cycle and was replaced. Another patient experienced a DLT, a grade 3 fatigue. Thus, the cohort was expanded by three additional subjects. One of these patients also experienced a DLT, a grade IV thrombocytopenia. As a result, no MTD has been determined yet, and the protocol is currently being amended to help establish the MTD of this combination treatment.

RESULTS

Table 1: Patient Demographics (n=19)

Median Age (years)	67 (range: 34-88)
Male: Female	12:7
ISS Stage (at study entry)	
I	5
II	10
III	4
Serum M-protein (g/dl)	
Median	2.80
Range	0.90 - 6.15
Urine M-protein (mg/24h)	
Median	132
Range	20 – 8458
Serum Creatinine (mg/dL)	
Median	1.0
Range	0.6 - 2.1

Table 2: Patient Responses (n=19)

Complete Response (CR) (no serum M-protein)	2*[a] (11%)
Very Good Partial Responses (VGPR) (≥ 90% decrease in serum M-protein)	0
Partial Response (PR) (50-74% decrease in serum M-protein)	2[a] (11%)
Minor Response (MR) (25-49% decrease in serum M-protein)	0
Objective Response (CR+VGPR+PR+MR)	**4 (21%)**
Stable Disease (SD) (change in M-protein ± 25%)	9 (47%)
Disease Control (CR+VGPR+PR+MR+SD)	**13 (68%)**
Progressive Disease (PD) (>25% increase in M-protein)	6 (32%)

*Both CRs were IF+ and were not confirmed by bone marrow biopsy.

[a]In the first cohort (10 mg panobinostat every MWF + 0.05 mg/kg melphalan on days 1-5) there was 1 PR. In the amended second cohort (20 mg panobinostat every MWF + 0.05 mg/kg melphalan on days 1, 3, 5) there were 2 CRs and 1 PR.

Table 3: Patient Status (n=19)

Active on LBH-Mel	**3**
Off-Study	**16**
Progressive Disease on LBH-Mel	9
Completed 8 Cycles or Reached Max Response	0
Adverse Event	6
Patient Withdrew Consent	1

Table 4: Survival of Evaluable Patients (n=19)

Remaining on Trial	3
Completed Trial w/ Nonprogressive Disease	0
Completed Cycles (n)	
Median	1
Range	1-6
Time to 1st Response (mo) (n=4)	
Median	1
Range	1-1
Time to Best Response (mo) (n=4)	
Median	1
Range	1-2
Duration of Response (mo) (n=4)	
Median	4
Range	2-4+
Time to Study Termination (mo) (n=19)	
Median	2
Range	0-6+
Time to Progression (mo) (n=15)	
Median	2
Range	0-6+
Overall Survival (mo) (n=19)	
Median	Undefined
Range	1-15+
Follow-up (mo) (n=19)	
Median	6
Range	1-15+

ADVERSE EVENTS

Grade 3 adverse events included:

- **Reversible neutropenias (n=7)**
- **Reversible thrombocytopenias (n=7)**
- **Reversible anemias (n=2)**
- **Fatigue/weakness (n=1)**
- **Forearm rash (n=1)**
- **Hypokalemia (n=1)**

Grade 4 adverse events included:

- **Reversible thrombocytopenias (n=2)**

Fatigue

- **Common adverse event**
- **All but one case (grade 3) were grade 1 or 2**

No incidence of QTc prolongation > 500 msec

SUMMARY

In this Phase I/II study evaluating the combination of low dose oral melphalan with panobinostat for patients with relapsed/refractory MM:

- **The most common ≥ grade 3 adverse events included reversible neutropenia and thrombocytopenia**
- **All cytopenias were reversible**
- **Fatigue was a common adverse event with all but one case either grade 1 or 2**
- **An encouraging response rate of 21% has already been observed in this relapsed and refractory population of heavily pretreated MM patients**
- **An expanded Phase II trial will be conducted using this combination once the MTD has been determined and schedule of dosing has been optimized**

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