Abstract

Large phase 3 studies combining histone deacetylase inhibitor s (HDACIs) with bortezomib have been hampered by GI intolerance, which has not been observed when combined with immunomodulatory drugs. This is a single center phase 2 study of panobinostat with lenalidomide and dexamethasone, a completely oral regimen.

20 evaluable patients treated with a median of 3 lines of prior therapy over a median of 4 years since diagnosis were enrolled. 16 patients (80%) were lenalidomide-refractory and 35, 45, and 50% were refractory to each of the following: pomalidomide, bortezomib, and carfilzomib respectively. High-risk molecular findings were present in 13 (65%) patients. The primary objective was to evaluate the best overall response rate (ORR).

Secondary objectives were to evaluate safety, response duration, and overall progression-free survival.

Methods

Inclusion criteria were patients with rel/ref MM, measurable disease (m spleen ≥ 3.0, ≥ 200 mg/bw, ≥ 10 mg/dL of additional ALG ratio), adequate performance status. organ function (Castr C ≥ 50), hematologic parameters (ANC ≥ 1.5 vs. ≥ 1.0, PLT ≥ 100k vs ≥ 75k if thrombocytosis < or ≥ 50% platelet count).

Results

Treatment options for patients with multiple myeloma (MM) refractory (ref) to immunomodulatory drugs and proteasome inhibitors are urgently needed. A promising strategy is the use of egpic agents such as the pan histone deacetylase inhibitor (HDAC) panobinostat (pan) to modulate the acetylation of histones and proteins involved in oncogenesis. Preliminary results with pan demonstrate synergy against MM cells when combined with dexamethasone (dex), lenalidomide (len), and bortezomib (btz) (Ocio EM et al. Haematologica. 2010).

Currently ongoing are correlative studies evaluating the changes associated with study treatment in centriole expression, the nuclear shuttle protein HR23B translation and construction of protein inhibitory VS RNA expression and genomics, as well as exploratory studies of changes in the tumor microenvironment.

Conclusions

In rel/ref MM patients, pan in combination with len and dex demonstrates durable responses comparable to other recently approved agents, even in len/ref patients with high-risk molecular findings, indicating the essential role of pan in attaining a response. These results suggest that pan modulates expression of genes to restore sensitivity to len.

Grade 3/4 toxicities (regardless of drug attribution) were primarily hematologic, with neutropenia (55%), thrombocytopenia (40%) and anemia (5%) respectively but were generally not associated with sequelae of infections or bleeding and manageable with GCSF and/or dose reductions.

References


Conflicts of Interest

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A Phase II, Single-Center, Open-Label Study of Oral Panobinostat in Combination with Lenalidomide and Weekly Dexamethasome in Patients with Multiple Myeloma

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Introduction

Background

The primary objective was to evaluate the best overall response rate (ORR).

Secondary objectives were to evaluate safety, response duration, and overall progression-free survival.

The median age was 64 years and the median number of lines of therapy were 3 (range 1–10) and for those that were lenalidomide refractory, 4. They were a median of 4 years from the time of diagnosis. High-risk molecular findings were present in 13 (65%) patients, including 10 with gain of 1q21 by FISH and 3 with del p53. Four of the patients with gain of 1q21 also had t(4;14).

15 patients (74%) were lenalidomide-refractory and others only had a minimal response (MR) to RVD induction. 7 (15%) of patients were also refractory to pomalidomide, bortezomib, and carfilzomib respectively. 10 (55%) had only achieved a minimal response (MR) or less as the best response during the last line of treatment.

A shown in Table 3, responses include complete remission (CR), 3 very good partial responses (VGPR), 5 partial responses (PR), 8 MRs, 2 stable diseases (SD), and 1 disease progression, for an ORR of 45% and clinical benefit rate (CBR) (ie or greater) of 85%, and disease control rate (DCR) (ie or greater) of 95%.

The median progression free survival (PFS) was 7.5 months.

The number of patients requiring dose reductions of len/pan respectively were 4/2 for neutropenia and 2/1 for thrombocytopenia. Neurotoxicity related to dose reduction included 1 len for fatigue, and 1 pan asymptomatic T wave inversions. 2 patients required dose reduction of dex due to mood alterations.

Importantly, no dosage were held or reduced for GI toxicities and other than 1 asymptomatic TFC prolongation, no patients discontinued therapy for toxicity. 1 other patient did not complete cycle 1 due to PD.

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Table 1: Study Drug Doses

Results (continued)

The median progression free survival (PFS) is 7.5 months.

Notably, there were no significant GI toxicities & primarily expected hematologic toxicities.

For patients who were len refractory, there were 3 VPGR, 3 PR, 7 MRs, 2 SD, and 1 PD for a 38% ORR, 81% CBR, 94% DCR with a median PFS of 6.5 months. Notably, 3 len refractory cases were on len/pan from months 14, 19, and 26+ months including 2 with gain of 1q21 that had attained VGPR.

Currently ongoing are correlative studies evaluating the changes associated with study treatment in centriole expression, the nuclear shuttle protein HR23B thought to be essential for response to HDAC inhibition, RNA expression and genomics, as well as exploratory studies of changes in the tumor microenvironment.