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Marizomib for CNS-Multiple Myeloma

Ashraf Badros MD[1] , Zeba Singh MD[1], Binod Dhakal MD[2], Young Kwok MD[1], Ann MacLaren PhD[3], Paul Richardson MD[4], Mohit Trikha PhD[3], and Parameswaran Hari MD[2]

[1]Greenbaum Cancer Center, University of Maryland School of Medicine, Baltimore, MD; [2]Division of Hematology/Oncology, Medical College Wisconsin, Milwaukee, WI; [3]Triphase Accelerator, San Diego, CA, [4]Dana Farber Cancer Institute, Boston, MA

Abstract

Marizomib, a natural marine product, is an irreversible proteasome inhibitor (PI) that has distinct advantages over the currently approved PIs in that it irreversibly inhibits all three enzymatic activities of the proteasome and has been demonstrated to cross the blood brain barrier. Several studies have demonstrated that marizomib (MRZ) penetrates and can be retained in the CNS and that it substantially inhibits proteasome activity in the brain: radiolabeled MRZ showed 30% CNS biodistribution compared with blood levels in rats; it elicits a significant anti-tumor effect in a rodent model of malignant glioma and pharmacological inhibition of proteasome activity has been observed in primate brains. MRZ is currently under clinical investigation in relapsed-refractory multiple myeloma and grade IV malignant glioma. CNS-multiple myeloma (MM) is a rare manifestation of extra-medullary disease with very limited therapeutic options. Its prevalence is increasing as anti-myeloma therapies become more effective at treating systemic disease, resulting in the CNS becoming a sanctuary site for the disease further highlighting the urgent unmet clinical need in this patient population.
MRZ has demonstrated encouraging activity in non-CNS-MM and has emerging clinical activity in glioma making it a potentially promising CNS-MM therapeutic intervention.

To date 3 patients have been treated under compassionate use protocol with MRZ for CNS-involved MM. Two of these patients have received sufficient doses of MRZ in combination with dexamethasone (DEX) to evaluate its activity in this indication. MRZ was dosed initially at 0.55mg/m^2 and then increased to 0.7mg/m^2 once tolerability had been established on the schedule currently in use on the glioma study (days 1, 8, and 15 of a 28 day cycle as a 10 minute infusion). Both patients, who had received prior cranio-spinal radiotherapy and intrathecal chemotherapy with no response, have tolerated MRZ well with no unexpected adverse events. The first patient had an 89% reduction in cerebrospinal fluid (CSF) plasmacytosis and 77% serum LDH reduction. After 5 months daratumumab was added to MRZ and further clinical improvement was observed (resolution of double vision and becoming fully ambulatory). Six months after MRZ initiation the patient progressed clinically and stopped treatment. Clinical symptoms disappeared in the second patient in the second month of MRZ with complete resolution of CSF plasmacytosis and CSF monoclonal spike. The patient is currently undergoing the 9th cycle of treatment with sustained resolution of saddle anesthesia and no further signs of cauda equina symptoms. Collectively, these cases provide preliminary evidence that MRZ may have utility as a therapeutic for CNS-MM and also demonstrate that combination of MRZ and daratumumab may provide benefit in this indication.

Background

MRZ is unique amongst proteasome inhibitors in its ability to penetrate the blood brain barrier

MRZ has demonstrated prior clinical activity in relapsed/refractory MM as a single agent and in combination with pomalidomide (POM) + low-dose DEX (NCT0210335)

MRZ has also demonstrated encouraging activity in combination with bevacizumab in recurrent glioma (NCT02903069)

Here we describe clinical experience treating 2 CNS-MM with MRZ under single patient compassionate use protocols

Results

Case 1

Patient History:

- 41yr old male, presented MM in Feb 2008. Prior therapies included CyBorD, ASCT, allogenic HCT, CFZ/POM/DEX, Panobinostat/BTZ
- Relapsed to the CNS in June 2015. Treatments included IT chemotherapy, cranio-spinal radiation with no response and the presence of additional lesions

Dosing

MRZ was administered as a 10 min IV push on days 1, 8, and 15 of a 28 day cycle
DEX was administered on the day of and day following MRZ dosing

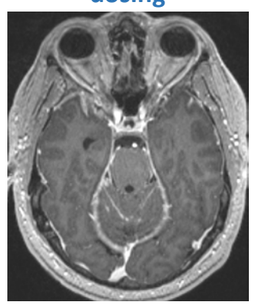
Cycle	IV MRZ (mg/m^2)	IV Daratumumab (mg/kg, weekly)	Oral DEX (mg)
1 & 2	0.55	0	20mg
3, 4 & 5	0.7	0	
6 & 7	0.7	16	

Clinical Results

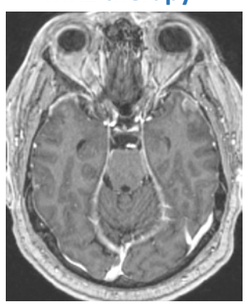
MRZ was well tolerated with no adverse events reported
By the end of cycle 2 of MRZ treatment a rapid and sustained clinical improvement was observed, with accompanying neurologic improvements:

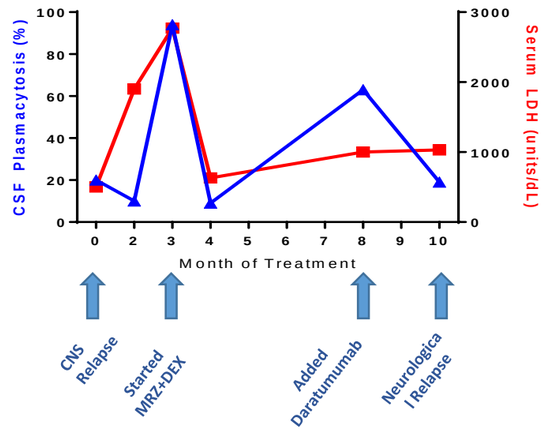
- Reduction in CSF plasmacytosis
- Reduced serum LDH
- Resolution of double vision
- Patient became fully ambulatory

MRI prior to MRZ dosing



MRI 2 months after MRZ therapy





- 6 months after initiating MRZ therapy, patient had a worsening of neurological symptoms and additional fractures and elected to stop therapy

Case 2

Patient History:

- 52yr old male, presented CNS-MM in Feb 2009. Prior therapies included RVD, ASCT, allogenic HCT, LEN
- CNS-relapse occurred in Jan 2016. Treatments included cranio-spinal radiation, POM/DEX, IT methotrexate with persistent CNS symptoms

Dosing

MRZ was administered as a 10 min IV push on days 1, 8, and 15 of a 28 day cycle
DEX was administered on the day of and day following MRZ dosing
Patient elected to add POM from cycle 8 onwards

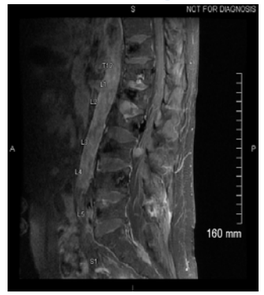
Cycle	IV MRZ (mg/m^2)	Oral POM (mg, D1-21)	Oral DEX (mg)
1 - 7	0.7	0	10mg
8 +	0.7	4	

Clinical Results

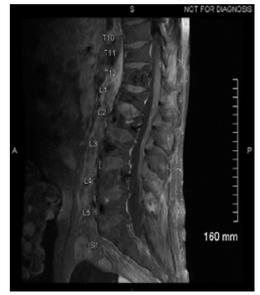
MRZ was well tolerated with no adverse events reported
By the end of cycle 2 of MRZ treatment clinical symptoms resolved and there was a complete resolution of CSF monoclonal spike

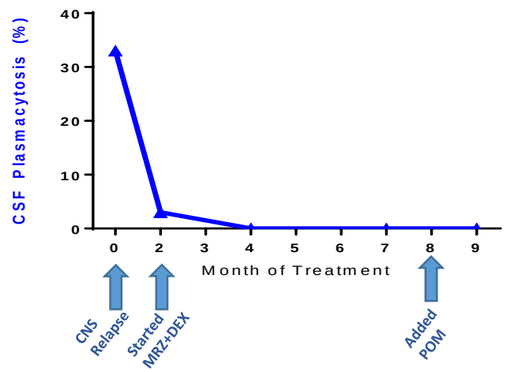
- No detectable disease in CSF following 2 cycles of MRZ
- Resolution of saddle anesthesia
- No further cauda equina symptoms

MRI prior to MRZ dosing



MRI 2 months after MRZ therapy





- Patient continues to be in a complete response in the CNS in cycle 9 and is tolerating treatment with MRZ + POM combination

Conclusions & Future Directions

- MRZ was well tolerated; no unexpected adverse events were reported in these patients
- These two cases further demonstrate that MRZ has clinical activity within the CNS and suggested that it should be further evaluated in CNS-MM