Marizomib for CNS-Multiple Myeloma

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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 emergent 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 initiating MRZ therapy, patient had a no further signs of cauda equina symptoms.

MRZ 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 initiation of 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 with sustained clinical improvement was observed, with accompanying neurologic improvements:

- Reduced serum LDH
- Resolution of double vision
- Patient became fully ambulatory

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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.