bjh short report

Marizomib for central nervous system-multiple myeloma

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Summary

Marizomib, a natural marine product, is an irreversible proteasome inhibitor currently under investigation in relapsed-refractory multiple myeloma (RRMM) and malignant glioma. Central nervous system-multiple myeloma (CNS-MM) is a rare manifestation of extra-medullary disease with few therapeutic options, highlighting the unmet clinical need in these patients. Marizomib demonstrated encouraging activity in RRMM and has emerging clinical activity in glioma, making it a potential CNS-MM therapeutic intervention. Herein, we present two patients with RRMM and CNS involvement who benefited from marizomib-based therapy. These cases provide the first proof of principle for further exploring marizomib in CNS-MM patients.

Keywords: multiple myeloma, central nervous system relapse, clinical studies, marizomib.

The outcome of therapy for patients with multiple myeloma (MM) has significantly improved with the introduction of immunomodulatory (IMiD®) agents, proteasome inhibitors (PIs) and monoclonal antibodies. However, extra-medullary relapse including central nervous system (CNS) involvement continues to confer poor prognosis (Katodritou *et al*, 2015). CNS-MM is a rare manifestation of extra-medullary disease in MM patients, which has increasing prevalence with more effective treatment of systemic disease. It is characterized by the presence of neoplastic plasma cells in the cerebrospinal fluid (CSF) and lepto-meningeal involvement (Abdallah *et al*, 2014; Lasocki *et al*, 2015). Neurological symptoms usually do not correlate with magnetic resonance imaging (MRI) findings, which can be normal, or with the extent of plasmacytosis. CNS-MM is a terminal event in many patients, with a median survival of less than four months (Fassas *et al*, 2002; Jurczyszyn *et al*, 2016). This may be related to a lack of effective intrathecal therapy (IT), the limited activity of radiotherapy (RT), as well as the limited availability of blood brain barrier (BBB) penetrating systemic therapies (Gangatharan *et al*, 2012).

Marizomib, a novel irreversible proteasome inhibitor, has demonstrated promising anti-myeloma activity in highly refractory MM patients (Richardson *et al*, 2016). Several studies have demonstrated that marizomib localizes to the CNS and significantly inhibits proteasome activity in the brain; radiolabelled marizomib showed 30% CNS biodistribution compared with blood levels in rats; it elicits a significant anti-tumour effect in a rodent model of malignant glioma; and pharmacological inhibition of proteasome activity has been observed in primate brains (Di *et al*, 2016). Recent data from an ongoing phase 1 trial in malignant glioma evaluating weekly dosing demonstrates that marizomib is well tolerated and shows promising anti-tumour activity (Bota *et al*, 2016). The clinical activity of marizomib in MM, together with its ability to penetrate the CNS, makes it a potential therapeutic agent for CNS-MM. We present two patients with refractory CNS-MM who benefited from marizomib-based therapy.

Case 1

A 32-year-old man presented with severe back pain leading to diagnosis of IgA kappa MM in February 2008. At presentation, he had 70% plasma cells in the bone marrow with a complex karyotype (deletion of 13q and 17p, and gain of 1q). He received 4 cycles of cytoxan, bortezomib and dexamethasone (CyBorD), followed by melphalan and autologous stem cell transplantation (ASCT) achieving a very good partial response (VGPR). Thalidomide and bortezomib maintenance was continued for 1 year, followed by daily thalidomide (50 mg). In May 2010, his disease progressed and he received lenalidomide and dexamethasone with no response. Subsequent CyBorD treatment resulted in a partial response. In March 2011 he received a second ASCT followed in August 2011 with allogeneic haematopoietic cell

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transplantation (allo-HCT) from a matched sibling after non-myeloablative conditioning (melphalan and fludarabine). Graft- versus-host disease (GVHD) prophylaxis consisted of mycophenolate mofetil and tacrolimus; he had limited chronic sclerodermatous lesions on the skin achieving a complete remission. In March 2014, he presented with a non-secretory relapse with multiple active lytic bony lesions on positron emission tomography (PET)/computed tomography (kappa restricted plasma cells on biopsy) and received carfilzomib, pomalidomide, and dexamethasone, achieving a negative PET before relapsing with a pathological fracture (left humerus) requiring placement of a rod and radiation in March 2015. Three cycles of panobinostat and bortezomib were received with no response, and subsequent development of plasmacytomas with multiple fractures in the ribs required radiotherapy for pain control.

In June 2015, he presented with severe headaches, numbness of the chin and visual changes. MRI suggested leptomeningeal lesions and the CSF was positive for kappa-restricted plasma cells with elevated protein and normal glucose (Table I). He started IT chemotherapy (methotrexate 12 mg, cytarabine 50 mg, prednisone 100 mg) twice weekly for 4 weeks, with worsening neurological symptoms (headaches, double vision and inability to walk) followed by cranio-spinal radiation (5000 cGy) and continued weekly IT chemotherapy. He had a transient clinical improvement, with rapid deterioration and worsening neurological symptoms, including hoarseness, difficulty swallowing, double vision requiring an eye patch, and he was unable to walk without support. He received further localized radiation to the brain and IT therapy was increased to three times weekly, with no response. MRI now showed additional lesions (Fig 1A).

Beginning in October 2015, he received marizomib on compassionate use protocol (IND 128147) at 0·55 mg/m^2 over 10 min weekly × 3; cycle repeated every 4 weeks for 2 cycles and then the dose was increased to 0·7 mg/m^2, at which time he demonstrated rapid and sustained clinical improvement. Although CSF plasmacytosis persisted at a low level, serum lactate dehydrogenase decreased. In February 2016, 5 months after initiating marizomib therapy, he had an enlarged axillary lymph node, which on histology revealed an extramedullary plasmacytoma with CD38$^+$ plasma cells. Daratumumab (16 mg/kg weekly × 2 months) was added with continued marizomib (Lonial *et al*, 2016). Neurologically, there were further improvements; he was able to remove the eye patch with resolution of the double vision and became fully ambulatory. However, by April 2016, 6 months after initiation of marizomib therapy this clinical picture deteriorated with worsening of neurological symptoms and more bony fractures. Interestingly, CSF plasma

Table I. Summary of CNS-MM symptoms and therapeutic interventions for Case 1 and Case 2.

Case 1 CNS-MM	Diagnosis	2 months	3 months	4–7 months	8 months	10 months +
Symptoms	Headache Chin numbness	Minimal improvement	Worsening: Double vision, inability to talk	Complete resolution of symptoms	Axillary lymph node Cytoplasmic kappa with surface expression of CD138/38/56	Worsening neurological and systemic symptoms
CSF						
Total protein	103	50	109	59	60	100
Plasmacytosis	20%	10%	94%	9%	63%	19%
Flow cytometry	+CD138/38	Positive	Positive	Positive	Positive	CD138$^+$/38 − (lost expression of CD38)
Serum LDH (u/l)	0·5	1·9	2·77	0·63	1·0	1·03
Therapy	Intrathecal	Craniospinal XRT	Marizomib + dexamethasone		+ added daratumumab	

Case 2 CNS-MM	Diagnosis	2 months	3–6 months	
Symptoms	Hand/arm weakness Ataxia Sexual symptoms	Minimal Improvement	Complete resolution of symptoms	Patient currently on third cycle of marizomib + dexamethasone and doing well
CSF				
Total protein	195	30	35	
Flow cytometry	+CD138/38 cells	Not determined	Negative	
M protein	33%	3%	Negative	
Therapy	Craniospinal XRT	Intrathecal	Marizomib + dexamethasone	

CNS-MM, central nervous system-multiple myeloma; CSF, cerebrospinal fluid; LDH, lactate dehydrogenase; XRT, radiotherapy.

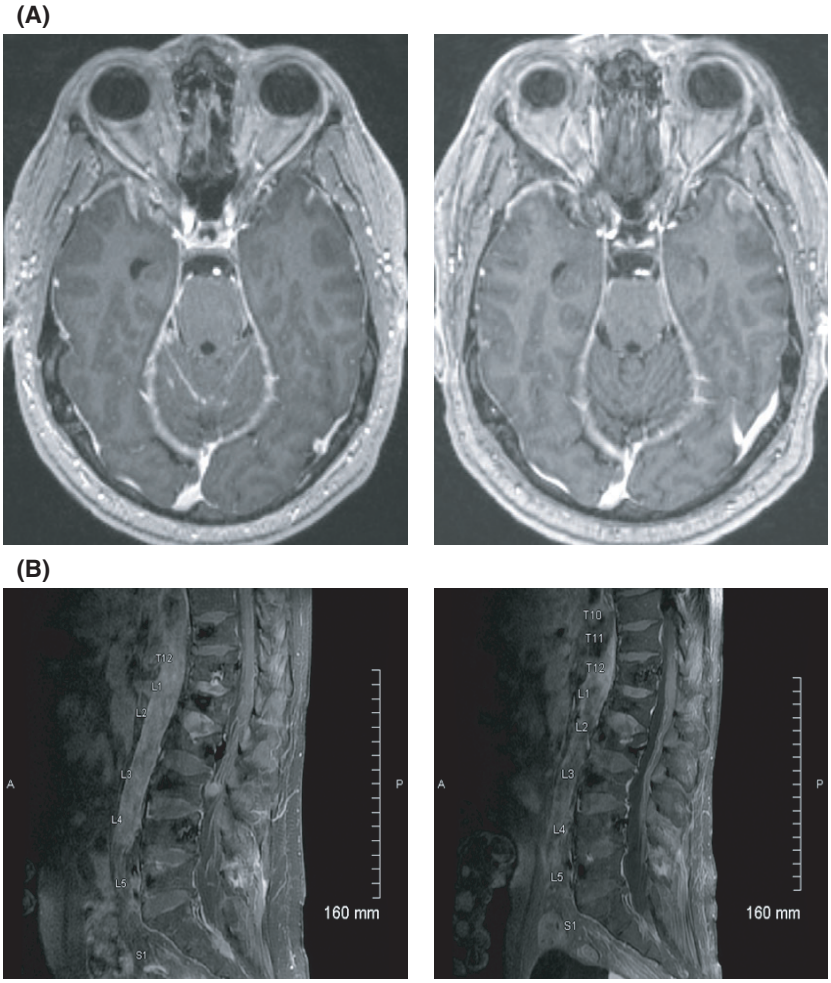

Fig 1. Magnetic resonance imaging findings before (left images) and 2 months after marizomib therapy (right images) in (A) Case 1 (head) and (B) Case 2 (lumbar spine).

cells at this time remained negative for CD38. The patient elected to stop therapy and was referred to hospice for comfort care.

Case 2

A 52-year-old man was diagnosed with IgG lambda MM (ISS III) in February 2009. He presented with back pain related to vertebral compression fracture. A bone marrow biopsy showed 90% involvement with lambda-restricted plasma cells. This patient had high-risk cytogenetics, including hypodiploidy and deletion of chromosomes 13, 14, 17, 18 and 22. He received three cycles of lenalidomide, bortezomib and dexamethasone (RVD) followed by high dose melphalan and ASCT, achieving a VGPR. With high-risk disease, he underwent matched sibling allo-HCT in December 2009 after non-myeloablative conditioning (total body irradiation 200 cGy). GVHD prophylaxis consisted of mycophenolate and ciclosporin; immunosuppression was stopped by August 2010 and he started lenalidomide (10 mg/day) maintenance (March 2010). He achieved a stringent complete response for 5 years at which point lenalidomide maintenance was discontinued (March 2015).

In November 2015, a biochemical progression was documented (monoclonal protein IgG lambda in the serum at 2·8 g/l). The patient was asymptomatic so no treatment was offered. In January 2016, he presented with weakness and numbness of hands with inability to write and perform fine motor functions. He rapidly developed loss of balance, gait incoordination and increasing pain in his lower back. On neurological examination he had perineal/saddle anesthesia, but no bowel or bladder incontinence. Serum monoclonal protein at that time increased to 4·1 g/l. CNS involvement was confirmed with the MRI of the spine showing new abnormal enhancing epidural soft tissue (Fig 1B). Lumbar puncture confirmed CNS-MM with detection of plasma cells (Table I). He received craniospinal irradiation (5000 cGy) with pomalidomide and dexamethasone, which was associated with minimal improvement in the back pain but persistent weakness of the hands and saddle anesthesia. He received 1 dose of intrathecal methotrexate with persistent CNS symptoms. Marizomib was given on compassionate use

protocol (IND 130840) at 0·7 mg/m^2 as a 10-min IV infusion on days 1, 8 and 15 along with dexamethasone on a 28-day cycle. After 2 cycles of marizomib, the patient's clinical symptoms disappeared; with sustained complete resolution of CSF plasmacytosis and CSF monoclonal spike. MRI of the spine showed improvement in epidural enhancement. The patient continues to do well and is currently undergoing the fourth cycle of treatment with sustained resolution of saddle anesthesia and no further signs of cauda equina symptoms.

Discussion

In both cases, patients suffered CNS relapse of MM after allo-HCT. In the first case, the relapse occurred after progression on multiple lines of therapy in the setting of extramedullary disease while in the second case, disease was mainly confined to the CNS. After IT chemotherapy and cranio-spinal radiation, both patients had transient responses followed by rapid deterioration (Case 1) and persistent symptoms (Case 2). Both patients thus had no remaining therapeutic options.

Given the CNS activity of marizomib, the drug was obtained on a compassionate basis to treat both patients, demonstrating clinical improvement in neurological symptoms and an objective reduction in CSF plasmacytosis in Case 1 and eradication in Case 2, with radiological improvements in leptomeningeal disease, coupled with improvement in quality of life. Both patients tolerated marizomib well, with neither exhibiting any adverse events. The discordance between clinical improvement in neurological symptoms and clearance of the CSF and radiological images in our patients are intriguing. There is no consensus on the best assessment of response in CNS-MM. Lastly, the disappearance of CD38 from the malignant plasma cells after the addition of daratumumab in Case 1, suggests that daratumumab may also cross the BBB. However, this needs to be confirmed in future studies.

These cases provide additional evidence for the CNS activity of marizomib, and underscore the need for further evaluation of this drug in CNS-MM. Although limited, our data demonstrate that a combination of marizomib and daratumumab might also be worthy of further exploration in CNS-MM.

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Authorship contribution

AZB and PH treated Case 1 and 2 respectively, held the IND, collected the data and wrote the first draft of the manuscript: ZS, BD, YK collected the data. MT provided the drug, advised on dosing schedule and the study design. PGR reviewed the data and helped with editing the manuscript. AM and MT helped with writing the manuscript. All the authors approved the final version before submission.

Conflict-of-interest disclosure

AB, ZS, YK, BD, PH, had no relevant conflict to declare. P.G.R. serves on advisory committees of and receives research funding from Celgene Corporation and Millenium (The Takeda Oncology Company). AM and MT are employees of Triphase Accelerator and hold stock.

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