Abstract

Background. CNS myeloma is a rare manifestation of multiple myeloma and is often associated with a dismal prognosis; however, cases are increasing in frequency as overall survival improves for MM. There is currently no standardized treatment for CNS myeloma; however, different chemotherapy and radiotherapy regimens have been described.

Methods. We had previously reported on the efficacy of proton-based craniospinal irradiation in a patient with CNS myeloma; here we present a patient with a history of extramedullary plasmacytoma, 10 years in remission status post standard systemic chemotherapy, with biopsy-proven CNS myeloma successfully treated with systemic chemotherapy as a first-line treatment.

Results. The patient achieved clinical and radiographic remission on 2 separate occasions with systemic chemotherapy alone.

Conclusions. This case demonstrates that systemically administered agents may have activity in CNS myeloma. Further investigations are necessary to establish the optimal combination of agents and treatment schedules.

Key Points

• In one instance, a patient with CNS myeloma was treated with systemic chemotherapy and novel agents to achieve complete remission on 2 separate occasions; remission was achieved on a third occasion following craniospinal irradiation.

• There may be a subset of patients with CNS myeloma in which systemic chemotherapy and novel agents can be used as a first-line option while withholding radiotherapy.

CNS myeloma is rare and is seen in approximately 1% of patients with multiple myeloma (MM); the prognosis for these patients, especially those with leptomeningeal spread, is dismal.\textsuperscript{1,2} Patients with CNS myelomatosis have an average survival of 2 months (range 0.1-25 months); a review of the literature has shown that up to 29.4% of patients had previously achieved complete remission.\textsuperscript{2,3} Review of one series showed a median of 8.5 months from initial diagnosis of MM to development of CNS MM.\textsuperscript{1}

The genesis of CNS MM has not been definitively determined; however, some authors have suggested hematogenous dissemination of plasma cells and direct extension from lytic lesions of the calvarium as possible routes of CNS invasion.\textsuperscript{1,4-6} Some series have noted a possible correlation between CD56 negativity and escape of myeloma cells from the bone marrow over time possibly leading to extramedullary myeloma and CNS myelomatosis.\textsuperscript{7-9} Autopsy reports have shown diffuse dissemination of plasma cells throughout the...
Importance of the Study

To the best of our knowledge, this is the first reported instance of a patient with CNS myeloma to achieve complete remission following systemic chemotherapy combined with a novel agent in the absence of radiotherapy. Additionally, this result was achieved not once but twice, despite partial treatment adherence. As of this writing, there is no standardized treatment regimen for patients with secondary CNS myeloma and as the median overall survival of patients with multiple myeloma continues to improve cases such as these will become more frequent. This paper serves as a starting point for identifying first-line systemic agents that minimize toxicity and are therapeutically effective in this population. Furthermore, this case raises the question as to why this particular patient was so responsive and if there are generalizable tumor or patient characteristics that might predict this response in others.

Case Presentation

The patient is a 56-year-old man with a history of extramedullary gastric plasmacytoma (diagnosed 2008, bone marrow biopsy negative), status post 5 cycles of lenalidomide, bortezomib and dexamethasone chemotherapy in complete remission since 1/2009. 10 years later on 6/24/19, the patient presented with 2 weeks of headaches, diminished concentration, slowed speech and flattened affect with multiple intracranial metastases discovered on MRI of the brain (Figure 1). The patient underwent a left frontal craniotomy for biopsy (7/2019); flow cytometry of the brain mass was negative due to low cell viability (11%), however, immunohistochemistry (IHC) was positive for CD138, aberrant CD3, and lambda light chain restriction consistent with metastatic plasmacytoma (Figure 6). A lumbar puncture was performed 2 weeks after the brain biopsy with IHC showing CD138+ cells and flow cytometry showed 15.9% clonal, CD38+ plasma cells supporting the diagnosis of recurrent CNS myeloma with leptomeningeal spread. A complete systemic workup, including bone marrow biopsy, spinal imaging, and myeloma laboratories were negative. The patient was started on pomalidomide and dexamethasone (7/24/2019) with regression of disease on subsequent MRI brain studies.

He did well until 5/2020 when interval imaging showed leptomeningeal enhancement; repeat bone marrow biopsy at that time was negative, however, serum lambda light chain paraproteins were elevated, and CSF analysis confirmed leptomeningeal disease (Figure 2). Treatment with daratumumab, Selinexor, and dexamethasone was started 9/2020. Subsequent MRI brain 9/27/2020 showed a complete response to treatment (Figure 2).

The patient worsened clinically over the ensuing month and a repeat MRI brain (11/2020) demonstrated progression of leptomeningeal disease. IT cytarabine was added to his chemotherapy regimen starting 12/1/2020 until 12/31/2020 at which point the patient opted to cease all further IT cytarabine injections. He then underwent autologous stem cell transplant with carmustine and thiopeta...
between 30% and 40%; these concentrations appear to be sufficient for clearance of malignant cells in lymphoma and myeloma.

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The patient then underwent CSI (36.23 D$_{RBE}$ in 18 fractions) from 5/2021 to 6/2021 with a total resolution of all craniospinal disease (Figures 4 and 5). The patient remains on Selinexor and pomalidomide following CSI and has noted significant improvement in his gait and processing speed. Of note, β2-microglobulin levels were obtained for the first time on 1/13/21 and at several time points thereafter during the course of his disease, however, these were never elevated.

**Discussion**

No generalizable conclusions can be drawn from the study of a single patient; we cannot universally apply our findings to other patients with CNS myeloma, nor can we be certain if the responses we observed were due to the independent or combined effects of the therapies employed. Despite these issues, the patient did have 1 significant sustained remission following pomalidomide/dexamethasone systemic therapy followed by a second shorter remission after daratumumab/Selinexor/dexamethasone systemic therapy.
In and of itself, the fact that the patient did respond robustly to these treatments in the absence of concomitant radiotherapy and IT chemotherapy suggests that there may be a subset of patients in which sustained remission might be achievable with systemic treatment alone as a first-line option. Furthermore, this raises the question of whether there is something unique about this patient’s malignancy that contributed to the robust response that was observed, or perhaps some intrinsic or acquired physiologic change that occurred following exposure to the therapeutic agents. Further investigation is necessary to determine if what we have observed can be recapitulated in other patients and if there are tumor and/or patient biomarkers that may be predictive of sensitivity to systemic agents. This could be useful if some reliable predictor of responsiveness to systemic therapies could be identified as it would permit patients to be stratified into groups in which radiation could potentially be held in reserve thereby minimizing toxicity.

The capacity to penetrate the BBB appears to be important in the treatment of CNS myeloma. This patient was treated with Selinexor, an XPO-1 inhibitor which has been shown to have excellent CNS penetration in animal models with brain:plasma ratios of 0.72 in rats and 0.61 in cynomolgus monkeys in 1 pharmacologic study.21 Furthermore, Selinexor has shown significant therapeutic efficacy in clinical trials in patients with relapsed diffuse large B-cell lymphoma (DLBCL) as well as in patients with glioblastoma; a recent phase II study in patients with recurrent glioblastoma showed partial response in 17% of patients and stable disease in 33%.21–23 Furthermore, maintenance therapy with CNS-penetrating agents appears important for the prevention and treatment of relapsed disease; for example, lenolinamide has been used as maintenance therapy in elderly patients with primary central nervous system lymphoma (PCNSL) following induction therapy in which the median duration of treatment exceeded 18 months and median progression-free survival was not reached.24 Selinexor was used as maintenance therapy in the case of a patient with refractory secondary central nervous system lymphoma (SCNSL) for 5 months resulting in complete remission, however, side effects of grade 3 fatigue and grade 2 anorexia necessitated cessation of Selinexor; the patient presented with impaired vision 3 weeks after cessation of Selinexor with MR showing the progression of his disease with spread to the optic apparatus.25

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Furthermore, Selinexor has shown significant therapeutic efficacy in clinical trials in patients with relapsed diffuse large B-cell lymphoma (DLBCL) as well as in patients with glioblastoma; a recent phase II study in patients with recurrent glioblastoma showed partial response in 17% of patients and stable disease in 33%.

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A review of the literature seems to indicate that bortezomib is ineffective in the treatment of CNS myeloma likely due to poor CNS penetration, however, an analogous proteasome inhibitor, marizomib, does appear to be able to penetrate the BBB with 30% bioavailability in the CSF. A case report of 2 patients with refractory CNS myeloma treated with marizomib showed promising results with complete sustained remission in 1 patient and initial

Figure 3. T1 post-contrast MRI brain studies showing recurrence with leptomeningeal disease: (a) left parietal, (b) left frontal, (c) left frontal; rapid progression was seen on follow-up scan, (d-f) multifocal areas of leptomeningeal enhancement.

Figure 4. (a-c) Axial T1 post-contrast MRI brain studies showing total resolution of leptomeningeal disease after treatment following recurrence.
response with relapse in the other; notably, the CSF of the patient with progression who had also been treated concomitantly with daratumumab showed plasma cells that were negative for CD38. Another case report in which daratumumab therapy was used in conjunction with CSF and IT MTX/cytarabine/hydrocortisone therapy resulted in sustained remission.

IT chemotherapy has been used in combination with systemic chemotherapy, immunomodulatory agents, or both with some success reported at the case series level for CNS myeloma, however, no large-scale randomized control study has been conducted yet. One case series of 17 patients showed improvement in overall survival of 2-20 months in patients treated with IT chemotherapy compared to those who did not, however, each patient was treated with variable systemic chemotherapy regimens.

Plasma cells are known to be radiosensitive, consequently, CSI has been used often for the treatment of disseminated CNS myeloma with the literature showing an association between radiotherapy and prolonged overall survival; reports have shown a median survival of 3 months in patients treated with radiotherapy vs 0.81 months for those who did not undergo radiotherapy. Hematologic toxicity secondary to CSI is magnified in patients who have already received chemotherapy prior to radiation; severe myelosuppression has been reported to be as high as 47% in patients that had previously received chemotherapy prior to CSI for CNS myeloma as compared to 5% in those who had not had prior chemotherapy. Our group has previously reported a case of a patient with CNS myeloma in whom proton therapy was successfully used in combination with pomalidomide and dexamethasone used to achieve a durable remission with no long-term hematologic sequelae and minimal acute toxicity. Prior studies in adults with medulloblastoma showed that proton beam CSI was associated with significantly reduced rates of

Figure 5. T1 post-contrast MRI cervical spine studies showing (a) recurrence with leptomeningeal carcinomatosis predominately along the dorsal cervical thecal sac and (b) post-treatment resolution of the leptomeningeal enhancement.

Figure 6. (a) Frozen section of left frontal mass showing mitotic figures and plasma cells. (b) Low power magnification, H&E, brain-tumor interface. (c) ×10 H&E, interface of tumor and brain. (d) Lambda light chain restriction. (e) Positive MUM1 immunohistochemical stain.
hematologic toxicity compared to traditional photon-based CSI (17% vs 48%, \( P = .04 \)); these findings are further reinforced by the low rates of hematologic toxicity (8%) in patients with disparate malignancies who were treated with proton-based CSI at M.D. Anderson Cancer Center.\(^{34,36}\)

As mentioned previously, some case studies have noted the depletion of CD38+ plasma cells in the CSF of patients treated with daratumumab; flow cytometry of patients’ tumor cells prior to and at intervals following targeted therapy may be helpful in determining patterns of resistance and susceptibility. Furthermore, larger patient cohorts with tissue and CSF banking provide opportunities for gene and RNA sequencing of resistant and susceptible clonal populations between different patients and within the same patient at different time points throughout treatment.

This patient demonstrated remarkable initial responses to several systemic chemotherapy regimens with radiographic regression of his CNS disease following the first- and second-line treatment regimens. Nonetheless, the robust remission we observed in the absence of concomitant IT chemotherapy and radiotherapy raises the question of whether there are patients with CNS myeloma that may be treated with systemic agents as a first-line regimen, thereby minimizing potential toxicity and reserving a second line of therapy in the event of relapse. As patients with MM continue to live longer the frequency of patients with secondary CNS myelomatosis and plasmacytoma will likely continue to rise; consequently, identification of effective standardized treatment regimens for this disease is becoming increasingly necessary. This case serves as a starting point for further investigation and identification of patients with CNS myeloma who may be responsive to systemic therapies.

**Keywords**

CNS myeloma | craniospinal irradiation | leptomeningeal | multiple myeloma

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