Patterns of Central Nervous System Involvement in Relapsed and Refractory Multiple Myeloma

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Abstract

Central nervous system (CNS) involvement in multiple myeloma (MM) usually in advanced relapsed/refractory setting. The current manuscript presents the largest published series of CNS MM cases with malignant cerebrospinal fluid analyses. This report highlights poor prognosis of CNS MM in the era of novel agents and paucity of agents with good CNS penetration.

Background: Invasion of CNS in MM is an extremely rare occurrence that is associated with advanced disease with poor prognosis. **Patients and Methods:** Our MM database identified 35 CNS MM cases presenting between January 1996 and March 2012. Descriptive analyses were performed on available data on patient characteristics, disease course, and outcomes. **Results:** The mean age at diagnosis was 55.4 years; 23.5% (n = 8) patients had elevated levels of beta-2-microglobulin > 5.5 mg/L; 68.6% (n = 24) of patients had elevated lactate dehydrogenase (LDH) levels (≥ 2 times upper limit of normal); and 14% (n = 5) of patients had secondary plasma cell leukemia. Magnetic resonance imaging (MRI), which was performed in 34 patients, showed diffuse or localized leptomeningeal disease in 20 patients (58.8%). Monoclonal malignant plasma cells were found by CSF analysis in all 35 patients. In total, 31 patients received chemotherapy, including intrathecal chemotherapy as a part of their treatment, with a median survival of 4 months after CNS MM diagnosis. **Discussion:** In our experience, CNS MM is an aggressive terminal disease feature associated with high beta-2-microglobulin level, high LDH level, and secondary plasma cell leukemia. This study highlights an unmet need in this subset of patients with high-risk, relapsed or refractory MM. **Conclusion:** Achieving adequate CSF penetration while limiting the off-target effects needs to be considered in MM-specific novel drug development.

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Introduction

Multiple myeloma (MM) is a mature B-cell malignancy that usually presents with neoplastic proliferation of plasma cells that secrete a monoclonal immunoglobulin detectable in the serum or urine, accompanied by variable degree of renal insufficiency, hypercalcemia, anemia, and recurrent infections.[1] The involvement of central nervous system (CNS) in MM occurs in 1% of cases, presenting in advanced stages of the disease and usually associated with a poor prognosis.[2,3] Patients with CNS involvement in MM (CNS MM) may present with focal neurological deficits, altered mental status, or cognitive impairment that eventually leads to a diagnosis based on detection of malignant plasma cells in the cerebrospinal fluid (CSF) cytologic analysis or leptomeningeal enhancement on magnetic resonance imaging (MRI).[4] Herein, we present a detailed descriptive analysis on the CNS MM cases seen at our institution.

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Patients and Methods

A retrospective analysis was performed on the University of Arkansas MM database to search for CNS MM patients. CNS MM was defined as patients presenting with symptoms suggestive of CNS involvement along with positive CSF cytology for malignant plasma cells. We identified 35 patients from a review of the cytology laboratory archive material; data were also retrieved from the cytogenetic laboratory database. All currently available (35/35) CSF

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cytologic specimens positive for malignant plasma cells were reviewed. The medical records of all such identified patients were reviewed. MRI imaging for these patients was also reviewed to characterize findings unique to CNS MM. Descriptive analyses were performed using Microsoft Excel.

Results

Clinical and Laboratory Characteristics

Table 1 presents the clinical characteristics of 35 patients with CNS MM. The median age at diagnosis was 72 years; the median interval from diagnosis of MM to development of CNS MM was 15 months (range, 3-121 mo). Of the 35 patients, 3 (8.6%) presented with CNS MM as a manifestation of disease relapse from complete remission (CR), whereas 15 patients (42.9%) already had relapsed disease and were progressing on therapy. The remaining 17 patients were receiving treatment for relapsed MM and responding (stable disease or better) at the time of CNS MM diagnosis. The most common symptoms associated with CNS MM were extremity weakness, confusion, and headache (Table 2). However, 2 patients were asymptomatic and were diagnosed during restaging with radiological findings confirmed with CNS MM with CSF cytologic findings of malignant plasma cells. Secondary plasma cell leukemia accompanied the diagnosis of CNS MM in 5 patients (14.3%). The immunoglobulin (Ig) isotype was variable with CNS MM patients: IgG was present in 16 patients (45.7%), IgA in 11 patients (31.4%), IgM in 2 patients (5.7%), nonsecretory MM in 3 patients (8.6%), and light chain both kappa and lambda in only 2 patients (5.7%); 1 patient (2.9%) had biclonal MM (IgG kappa + IgA kappa). Elevated beta-2-microglobulin (β2M) (> 5.5 mg/dL) and serum lactate dehydrogenase (LDH) levels were seen in 23.5% (n = 8) and 68.5% (n = 24) of patients, respectively. Gene-expression profiling (GEP) on $CD138^+$ cells from bone marrow aspirate samples were available for 20 patients at baseline (time of original diagnosis) as well as at relapse with CNS MM. Baseline GEP showed GEP-70 gene signature[5] high risk in 14.5% (n = 3) and GEP-80 gene signature[6] high risk in 10% (n = 2) of these 20 patients. GEP at time of relapse with CNS-MM showed GEP-70 high risk in 95% (n = 19) and GEP-80 high risk in 100% (n = 20).

Table 1 Characteristics of Patients With Multiple Myeloma With Central Nervous System Involvement

Gender, male:female	**19:16**
Age, years, median (range)	72 (32-80)
MM paraprotein, no. of patients (%)	
IgG	16 (45.7%)
IgA	11 (31.4%)
IgM	2 (5.7%)
Nonsecretory	3 (8.6%)
Biclonal	1 (2.9%)
Light chain	2 (5.7%)
Time from MM Diagnosis to CNS MM, mo, median (range)	15 (3-121)
Baseline ISS stage, no. of patients (%)	
Stage III	15 (42.8%)
Stage II	7 (20%)
Stage I	8 (23%)
Unknown	5 (14.2%)
Baseline serum LDH level, no. of patients (%)	
Serum LDH >190 mg/dL	15 (43%)
Serum LDH <190 mg/dL	9 (25.7%)
Unknown	11 (31.3%)
Baseline cytogenetic abnormalities, no. of patients (%)	
Normal	3 (8.6%)
Abnormal	18 (51.4%)
Unknown	14 (40%)
Baseline GEP-70 risk status (available for 20 patients)	3 (14.5%)
Primary plasma cell leukemia	6 (17.1%)
Serum LDH level at CNS MM diagnosis, no. of patients (%)	
Serum LDH >190 mg/dL	24 (68.6%)
Serum LDH <190 mg/dL	10 (28.6%)
Unknown	1 (2.8%)
Cytogenetic abnormalities at CNS MM diagnosis, no. of patients (%)	
Normal	9 (25.7%)
Abnormal	16 (45.7%)
Unknown	10 (28.6%)
GEP-70 risk status at CNS MM diagnosis	95%
Secondary plasma cell leukemia at CNS MM diagnosis	14.3%

Abbreviations: CNS MM = central nervous system multiple myeloma; CR = complete response; GEP = gene-expression profiling; Ig = immunoglobulin; ISS = International Staging System; LDH = lactate dehydrogenase; MM = multiple myeloma; nCR = near-complete remission; PD = progressive disease; PR = partial response.

CSF and Radiological Features

All 35 patients had morphological evidence of malignant plasma cells on CSF analysis (Fig. 1). Flow cytometry data of the CSF sample was obtained for 8 patients (22.8%), in which all samples were strongly positive for CD38 or CD138 (Table 3), 3 patients (37.5%) were positive for CD56, and 2 patients (25%) were positive for CD45. Magnetic resonance imaging (MRI) of the head was performed in 34 patients. MRI showed diffuse or localized leptomeningeal enhancement in 20 patients (58.8%), 9 patients (26.4%) did not have any signs of leptomeningeal disease, 3 patients (8.8%) had a combination of both leptomeningeal enhancement

Table 2 Neurologic Signs and Symptoms in Multiple Myeloma With Central Nervous System Involvement

Signs and symptoms	Number of patients
Limb weakness	13 (37%)
Confusion	10 (29%)
Headache	9 (26%)
Seizure	6 (17%)
Visual Disturbances	6 (17%)
Cranial nerve palsies	6 (17%)
Paresthesia	5 (14%)
Nausea/Vomiting	4 (11%)
Speech disturbances	2 (6%)
Paraparesis	2 (6%)
Urinary Incontinence	1 (3%)
Gait Disturbances	1 (3%)