RESEARCH ARTICLE

Central nervous system involvement by multiple myeloma: A multi-institutional retrospective study of 172 patients in daily clinical practice

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The multicenter retrospective study conducted in 38 centers from 20 countries including 172 adult patients with CNS MM aimed to describe the clinical and pathological characteristics and outcomes of patients with multiple myeloma (MM) involving the central nervous system (CNS). Univariate and multivariate analyses were performed to identify prognostic factors for survival. The median time from MM diagnosis to CNS MM diagnosis was 3 years. Thirty-eight patients (22%) were diagnosed with CNS involvement at the time of initial MM diagnosis and 134 (78%) at relapse/progression. Upon diagnosis of CNS MM, 97% patients received initial therapy for CNS disease, of which 76% received systemic therapy, 36% radiotherapy and 32% intrathecal therapy. After a median follow-up of 3.5 years, the median overall survival (OS) from the onset of CNS involvement for the entire group was 7 months. Untreated and treated patients had median OS of 2 and 8 months, respectively ($P < 0.001$). At least one previous line of therapy for MM before the diagnosis of CNS disease and >1 cytogenetic abnormality detected by FISH were independently associated with worse OS. The median OS for patients with 0, 1 and 2 of these risk factors were 25 months, 5.5 months and 2 months, respectively ($P < 0.001$). Neurological manifestations, not considered chemotherapy-related, observed at any time after initial diagnosis of MM should raise a suspicion of CNS involvement. Although prognosis is generally poor, the survival of previously untreated patients and patients with favorable cytogenetic profile might be prolonged due to systemic treatment and/or radiotherapy.
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Introduction

During recent years an increasing attention has been paid to extramedullary involvement by multiple myeloma (MM). At the time of diagnosis, extramedullary MM is found in ~7% of patients, while another 6% may develop extramedullary lesions later in their disease course [1]. However,

Additional Supporting Information may be found in the online version of this article.

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the central nervous system (CNS) is a very rare location of myelomatous involvement and is diagnosed in less than 1% of patients [2]. Consequently, the available data on CNS MM are extremely sparse and originate mostly from single case reports and retrospective studies on a limited number of patients. Therefore, data regarding characteristics, diagnosis, treatment algorithms and outcomes of patients with CNS MM are currently lacking.

We describe the clinical and pathological characteristics of 172 patients with CNS MM in an international retrospective analysis. We also present diagnostic methodologies, and therapeutic approaches and their impact on survival.

Methods

Patient Selection. This was a multi-institutional, retrospective study conducted in 38 centers from 20 countries in Europe (Belgium, Czech Republic, Denmark, France, Germany, Greece, Italy, Holland, Norway, Poland, Spain, Sweden), Asia (Hong Kong, Japan, Turkey), South America (Argentina, Brazil), Australia, the United States and Canada. Patients were identified through a database search at each of the participating institutions. Adult (≥18 years) patients with a pathological and/or radiological diagnosis of CNS MM between January 1995 and December 2014 were included. CNS involvement was defined as histological and/or radiological evidence of myeloma arising from the CNS in a location noncontiguous to bone.

Data Collection. Clinical data included age at the time of MM diagnosis and at the time of CNS involvement, ISS stage, cytogenetic abnormalities, time from MM diagnosis to CNS MM diagnosis, gender, number and type of therapies previous to CNS involvement, symptoms at the time of CNS MM diagnosis, magnetic resonance imaging (MRI) and computed tomography (CT) scan findings, number and types of therapies received for CNS MM, overall survival (OS) and cause of death. Laboratory data included: immunoglobulin isotype, beta-2-microglobulin (B2M), albumin, lactate dehydrogenase (LDH) levels at CNS MM diagnosis. Pathological data included findings in cerebrospinal fluid (CSF) cytology and flow cytometry.

Statistical Analysis. Continuous and categorical variables are presented using descriptive statistics. Time from MM diagnosis to CNS MM diagnosis and OS were estimated using the Kaplan-Meier method. The log-rank test was used to compare OS estimates according to prognostic factors. Univariate and multivariate survival models were fitted using the Cox proportional-hazard regression method. The outcome measure was hazard ratio (HR) with 95% confidence interval (CI). Univariate analysis (UVA) was performed for each variable, and only the variables with *P*-values <0.1 were included in the multivariate analysis (MVA). *P*-values <0.05 were considered statistically significant in the MVA. All calculations and graphs were obtained using STATA 13.1 (StataCorp LP, College Station, TX).

Results

Clinical Characteristics

A total of 172 patients met the predetermined criteria for inclusion in this study. The median age at diagnosis of MM was 53 years (range, 31 − 82 years), and the median age of CNS MM diagnosis was 56 years (range, 33 − 82 years). The median time from MM diagnosis to the development of lesions in the CNS was 25 months (range, 0 − 216 months; Fig. 1A). Thirty-eight patients (22%) were diagnosed with CNS involvement at the initial diagnosis of MM (primary CNS MM). The median number of prior therapies before CNS MM involvement was 2 (range, 0 − 8); 69% of previously treated patients had received alkylators, 59% IMIDs, 58% proteasome inhibitors, 54% autologous SCT and 5% allogeneic SCT. The most common symptoms at presentation were visual changes (36%), radiculopathy (27%), headache (25%), confusion (21%), dizziness (7%) and seizures (6%). Selected clinical characteristics are shown in Supporting Information Table 1.

Imaging Studies

MRI of the brain and/or spine was performed in 156 patients (91%) showing evidence of disease in 145 of them (93%). CT scans of the brain and/or spine were performed in 53 patients (31%), and showed evidence of disease in 43 of them (81%). No MRIs or CT scans were performed in 5 patients (3%). Out of 167 patients who underwent MRI and/or CT, leptomeningeal involvement was identified in 95 patients (57%) and a intracranial mass lesion in 89 patients (53%); leptomeningeal involvement only was identified in 63 patients (38%), mass only in 57 (34%), mass and leptomeningeal involvement in 32 (19%), and no mass or leptomeningeal involvement in 15 (9%).

Pathological Features

CSF cytology was performed in 96 patients (56%), and showed evidence of atypical and/or anaplastic plasma cells in 86 (90%). CSF flow cytometry was performed in 80 patients (47%), and showed a monoclonal plasma cell population in 73 (91%). Positive expression of CD38 and CD138 was present in all cases. The CSF flow cytometry profile is shown in Supporting Information Table 1. In total, there were 103 patients with pathologically confirmed CNS MM; 58 (56%) by CSF flow cytometry and CSF cytology, 28 (27%) by CSF cytology alone, and 17 (17%) by CSF flow cytometry alone. There were no differences in age at MM diagnosis, age at CSN MM diagnosis, sex, heavy chain and light chain restriction, and ISS stage between the group with pathological confirmation of CNS MM and the group without pathological confirmation (data not shown). FISH analyses prior to the diagnosis of CNS MM were available for 122 patients (71%). The FISH profile in these patients is shown in Supporting Information Table 1.

Treatment and Causes of Death

Of the 172 patients in our study, 166 (97%) received initial therapy for CNS MM consisting of systemic therapy in 117 (76%) patients, radiotherapy in 56 (36%) patients, intrathecal therapy in 49 (32%) patients and steroids only in 5 (3%) patients; 1 (1%) patient underwent mass resection and 32 (21%) patients were given autologous or allogeneic SCT after induction phase. Systemic chemotherapy included: IMIDs in 50 (43%) patients, proteasome inhibitors in 39 (33%) patients and other chemotherapy regimens in 28 (24%) patients. Details on the type of initial CNS MM therapy are shown in Supporting Information Table 2. Seventy-three patients (44%) went on to receive second line therapy, 28 (17%) received third line therapy, and 1 (1%) patient received fourth line therapy. At the time of this report, 139 patients (81%) have died. The causes of death are shown in Supporting Information Table 2.

Survival Analyses and Prognostic Factors

After a median follow-up of 3.5 years, the median OS for the entire group was 6.7 months (Fig. 1B). The patients who received no treatment for CNS MM had a median OS of 2 months, and the treated patients had a median OS of 7 months (HR 1.1, 95% CI 0.99 − 1.22; $P = 0.07$). The 1-, 2-, and 3-year OS rates for treated patients with CNS MM were 38% (95% CI 31 − 46%), 24% (17 − 31%) and 15% (9 − 22%), respectively. We then evaluated the effect of initial salvage treatment of CNS MM on OS. Patients who received systemic therapy only and systemic therapy plus radiotherapy appeared to have better OS but the OS in patients in all the other treatment groups were not significantly different than the OS of patients who were not treated (Fig. 1C). We then divided patients into 2 groups: a group of patients who received systemic therapy (with or without intrathecal and/or radiotherapy; $n = 117$), and patients who received no systemic therapy (resection and radiotherapy, intrathecal therapy and radiotherapy, steroids only, radiotherapy only, intrathecal therapy only; $n = 49$). The median OS for patients who received systemic therapy vs those who received no systemic therapy was 12 months and 3 months, respectively (HR 0.44, 95% CI 0.29 − 0.65; $P < 0.001$; Fig. 1D).

In the univariate analysis, 1 or more lines of therapy for MM prior to CNS MM diagnosis vs. no previous therapy (Fig. 2A), ISS staging

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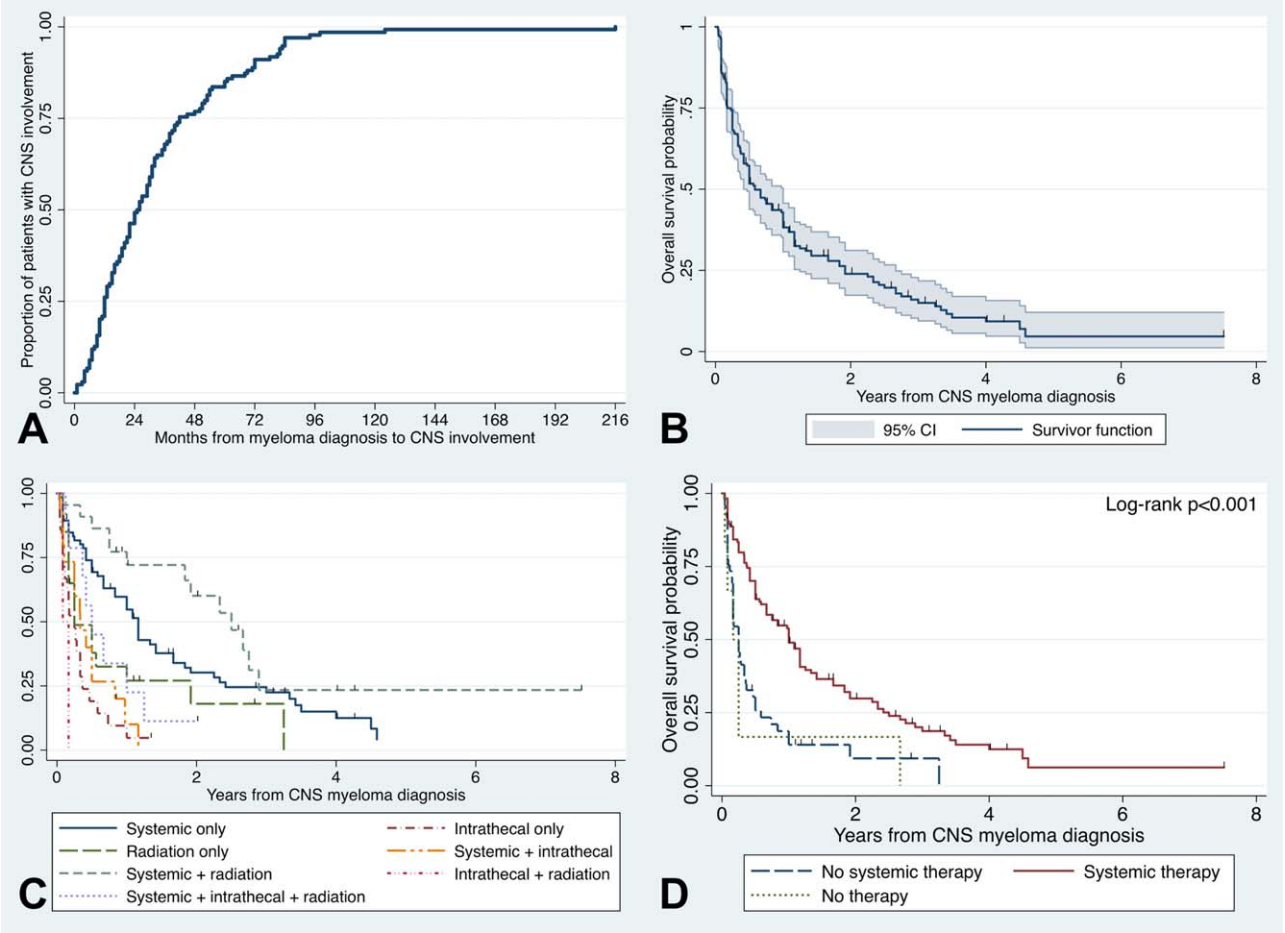

Figure 1. Time from MM diagnosis to diagnosis of CNS involvement by MM (A), and OS estimates in all patients with CNS MM (B), in patients treated with different types of therapy (C), and in patients received or did not receive systemic therapy (D). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

(Fig. 2B), >1 FISH abnormality vs. 0-1 abnormalities (Fig. 2C), and pathological confirmation of CNS MM vs. no pathological confirmation (Fig. 2D) were associated with a worse OS. Patients with mass/enhancement and mass/no enhancement in MRI or CT had a better OS than patients with no mass/no enhancement and no mass/enhancement (Fig. 2E). Age, sex and immunoglobulin isotype were not associated with worse or better OS. Although significant in the univariate model, elevated LDH level at CNS MM diagnosis was not included in the multivariate model because there were less than 100 observations. In the multivariate analysis, 1+ previous lines of therapy for MM vs. no previous therapy and >1 FISH abnormality vs. 0-1 abnormalities were independently associated with worse OS. The univariate and multivariate models are shown in Supporting Information Table 1.

Using number of previous lines of therapy prior to CNS MM diagnosis and number of adverse FISH abnormalities, we then generated a score in which patients were divided in three groups: a group with no previous therapies and 0-1 FISH abnormalities (0 risk factors; $n = 16$, 13%), a group with either >1 previous therapy or >1 FISH abnormality (1 risk factor; $n = 72$, 59%), and a group with >1 previous therapy and >1 FISH abnormality at diagnosis (2 risk factors; $n = 34$, 28%). The median OS for patients with 0, 1 and 2 risk factors were 25 months, 5.5 months (HR 2.25, 95% CI 1.20 − 4.20; $P = 0.01$) and 2 months (HR 4.65, 95% CI 2.33 − 9.26; $P < 0.001$), respectively (Log-rank for trend $P < 0.001$; Fig. 3A). In a subgroup sensitivity analysis, the increased score remained associated with shortened OS after removal of patients who were not treated (Fig. 3B), in patients who received systemic therapy (Fig. 3C), and in patients who did not receive systemic therapy (Fig. 3D). The univariate and multivariate analysis for overall survival in patients with CNS myeloma is given in Supporting Information Table 3.

Discussion

In the present study of 172 CNS MM cases, the median age of patients was 53 years, whereas the average age at myeloma onset is about 65 − 70 years old, which suggests that younger myeloma patients might be more prone to develop lesions in CNS. This observation is consistent with other reports [3,4]. The time elapsed between initial MM diagnosis and detection of CNS involvement was relatively short (median of about 2 years). Remarkably, we showed that 22% of patients had CNS involvement at the time of MM diagnosis (primary CNS MM). The remaining cases were associated with more advanced disease (secondary CNS MM) [3,5–7]. However, the distribution of ISS stage did not favor more advanced stages, which suggests that development of CNS MM might not be associated with advanced myeloma, but rather with other characteristics of the disease. Neurological symptoms documented in our patients were heterogeneous, and included supratentorial, meningeal, and spinal manifestations. The presence of these symptoms in MM patients not thought to be chemotherapy-related should prompt the investigation for CNS involvement. Hypercalcemia, uremia, paraproteinemia, and/or bone damage, however, can confound the symptoms [8].

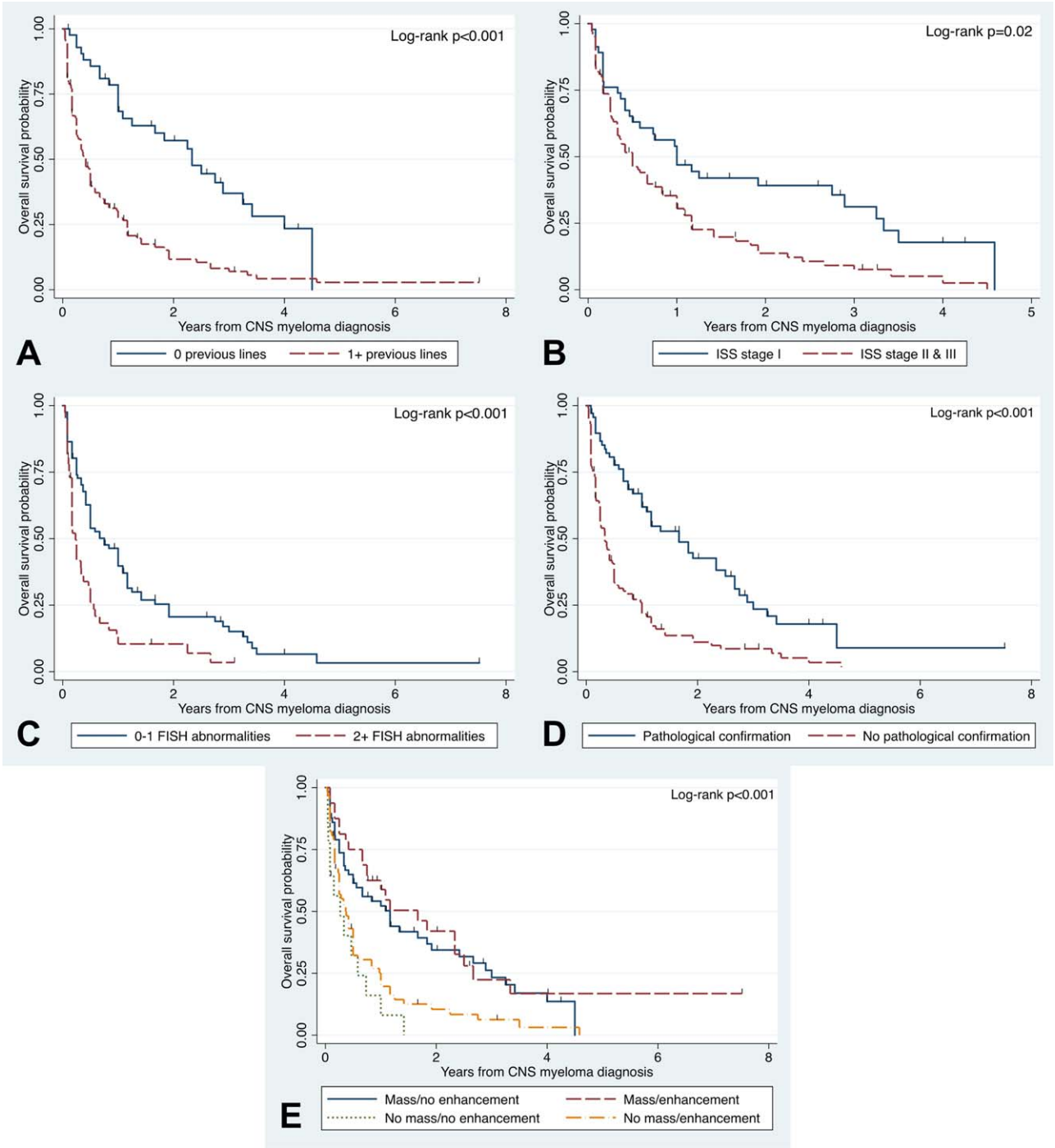

Figure 2. OS estimates in patients with CNS myeloma, according to previous lines of therapy (A), ISS stage (B), number of FISH abnormalities (C), pathological confirmation (D), and presence mass and/or enhancement on MRI/CT (E). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

We found IgA, IgD, and biclonal MM subtypes in 27%, 2%, and 1% of patients with CNS involvement, respectively. This distribution is consistent with previous reports [6,9,10]. Also, we found that deletions of 13q and 17p are the most frequent cytogenetic anomalies observed in patients with CNS MM. This is consistent with the observations from previous smaller studies [11,12]. Elevated LDH was one of the most common laboratory abnormalities present in our group. Although according to some authors, elevated activity of this enzyme may be linked to the risk of CNS MM [10], this association was not confirmed by other researchers [6]. Also, the lack of CD56 expression, an adhesion molecule of plasma cells, was postulated to play a role in CNS MM pathogenesis [12]. However, this hypothesis was not confirmed [13]; also the majority of our patients tested for this antigen showed negative expression on plasma cells isolated from CSF.

Detection of CNS MM on imaging studies can be challenging. The presence of mass and/or infiltration might be insufficient for establishing the diagnosis of CNS MM [11,14,15]. Contrast-enhanced MRI is more sensitive than CT and constitutes the method of choice in the detection of CNS MM [10,16,17]; however, it is associated with a false negative rate of 10% [6]. Therefore, it is preferable to perform imaging, pathological, and CSF examination concurrently. However, in daily clinical practice, it is not always possible to obtain specimen

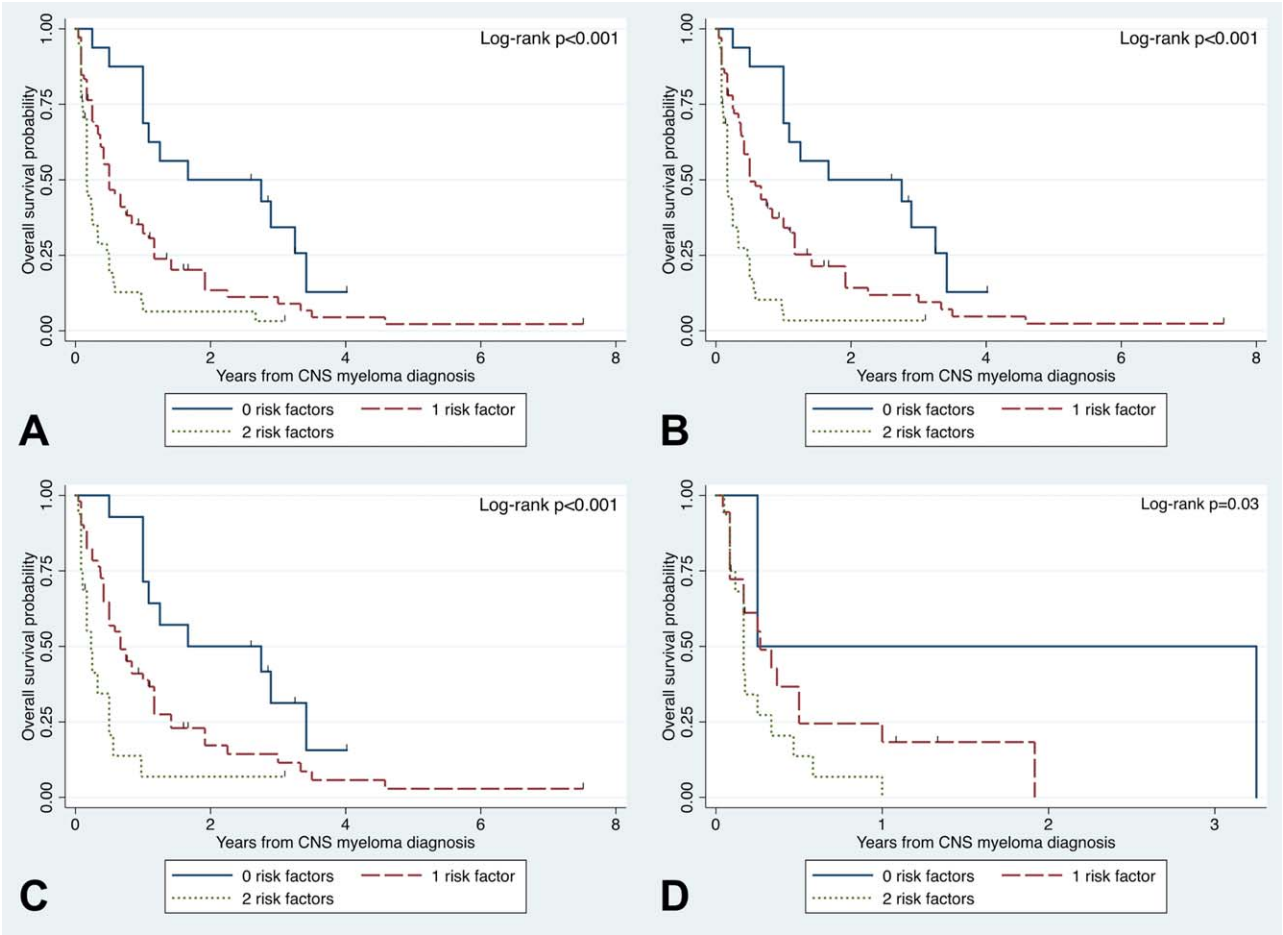

Figure 3. OS estimates in patients with CNS myeloma according to prognostic score for the entire group (A), in patients who were treated (B), in patients who received systemic therapy (C), and in patients who did not receive systemic therapy (D). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

for histopathological assessment due to poor performance status, end-stage disease or patient's refusal. The sole presence of plasma cells in CSF might not constitute a diagnosis of CNS MM [18]; however, in the right clinical setting, the presence of plasma cells in the CSF of a patient with myeloma should be highly suspicious of myelomatous CNS involvement. On the other hand, plasma cells can be absent in CSF from patients with parenchymal infiltration by myeloma or isolated changes in the dura mater [19]. Our study was retrospective and involved patients treated in different centers, which did not follow uniform diagnostic and treatment protocols. However, our data represents real-life routine practice and shows that the diagnosis of CNS MM can be suspected with limited number of diagnostic methods.

Data on treatment of CNS MM are sparse, and there is no standard of care in these cases. Our study showed that systemic treatment, alone or combined with radiotherapy, resulted in a significant improvement of survival in patients when compared to no systemic therapy. Due to marked heterogeneity of our group, we did not analyze the efficacy of specific treatments. Some anti-MM agents can cross the blood−brain barrier. Thalidomide, for example, can be detected in cerebrospinal fluid after oral administration at 100 mg/day [18,20]. However, the effects of thalidomide can be delayed constituting a limitation in patients with rapidly progressing CNS MM [21]. Animal studies showed that lenalidomide and pomalidomide could penetrate into the CNS as well [4,16]. One study showed that pomalidomide therapy resulted in disappearance of myelomatous cells from CSF [22]. The penetration of bortezomib through the blood−-brain barrier was limited in animal models [23]. Bendamustine can potentially be used in the management of CNS MM, as administration of this agent resulted in clinical improvement of patients with CNS lymphoma [24,25].

Intrathecal agents have been used in CNS MM with conflicting results [9,12,26–29]. The usefulness of intrathecal agents is often put into question as they are usually used in combination with systemic therapies [27], and might not be effective as monotherapy [28]. In our study, the patients treated only with intrathecal therapy or intrathecal therapy combined with radiotherapy had poor survival. Although whole brain radiation is a therapeutic option in CNS MM, its practical application is limited due to toxicity. Localized metastases to CNS can be treated with low-dose radiotherapy [10]. The role of autologous hematopoietic stem cell transplantation (HSCT) in the management of CNS MM is unclear. Some authors point to potential beneficial effects of high-dose melphalan conditioning prior to autologous HSCT [16,30].

Patients treated with systemic therapy combined with intrathecal and radiation therapy had poor outcomes when compared with systemic therapy only, but the number of patients who received such treatment was small and the data are probably biased. Altogether, our observations regarding treatment suggest that systemic therapy should constitute the basis of effective treatment of CNS involvement in myeloma patients. However, it should be emphasized that the data are retrospective and patients were selected to different treatment

strategies, which would include the selection bias that systemic therapy was chosen for more fit patients.

The survival of patients with CNS MM in our study is poor, which is consistent with previous findings [10,16]. However, long-term survivors have been reported [31,32]. Little is known on the prognostic factors in CNS MM. A study on 26 patients with CNS MM identified plasma cell labeling index and high-risk FISH abnormalities as adverse prognostic factors [33]. That study also showed poor survival in patients with myelomatous involvement of the CNS. We identified two significant predictors of unfavorable prognosis: at least one previous line of anti-MM therapy, and more than one cytogenetic abnormality in MM cells. The proposed scoring system seemed to maintain its significance in patients treated with more effective as well as less effective therapies, and should be validated independently.

Due to its retrospective character, our study is not free from potential limitations, such as incomplete documentation or lack of uniform diagnostic and therapeutic protocols. Since all the patients included in the analysis were treated at tertiary centers, our sample might be subject of selection bias and might not be representative of the whole population of CNS MM patients. Despite these limitations, our study is the largest analysis of CNS MM patients. Furthermore, due to the very low incidence of CNS MM, a prospective study of individuals with this condition is unlikely to be conducted.

In conclusion, the neurological manifestations not associated with chemotherapy-related toxicities observed in patients with MM should raise a suspicion of CNS involvement. The diagnosis of CNS MM should be based on imaging studies, CSF cytology and flow cytometry, supplemented with histopathological examination in doubtful cases. Although prognosis is generally poor, especially in patients with a long history of chemotherapy and unfavorable cytogenetic profile, survival of individuals free from these negative prognostic factors can be prolonged due to administration of systemic treatment. The administration of intrathecal therapy alone or in combination with radiotherapy might not be sufficient to improve prognosis and prolong survival. Prospective multi-institutional studies are warranted to improve the outcome of patients with CNS MM.

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