HHS Public Access

Author manuscript

Am J Hematol. Author manuscript; available in PMC 2017 July 09.

Published in final edited form as:

Am J Hematol. 2016 June ; 91(6): 575–580. doi:10.1002/ajh.24351.

Central Nervous System Involvement by Multiple Myeloma: a Multi-Institutional Retrospective Study of 172 Patients in daily clinical practice

A full list of authors and affiliations appears at the end of the article.

Abstract

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.

Keywords

multiple myeloma; therapy; central nervous system

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 approximately 7% of patients, while another 6% may develop extramedullary lesions later in their disease course [1]. However, the central nervous system (CNS) is a very rare location of extramedullary involvement and is diagnosed in less than 1% of MM patients [2]. Consequently, the available data on CNS MM are extremely sparse and originate mostly

Corresponding author: Artur Jurczyszyn, MD, PhD, Department of Hematology Jagiellonian University Medical College, 17 Kopernika Str., 31-501 Krakow, Poland; phone +48124247600, fax +48124247426, mmjurczy@cyf-kr.edu.pl.

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 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 histologically or radiologically proven plasmacytoma arising from the CNS in a location non-contiguous with a 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 hazard ratios (HRs) were calculated using the Cox proportional-hazard regression method. The outcome measure was the HR with 95% CI. For the logistic and survival regression models, 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, USA).

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; Figure 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 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 cerebral 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

FISH analyses prior to the diagnosis of CNS MM were available for 122 patients (71%). The FISH profile in these patients is shown in Table 1. CSF cytology was performed in 96 patients (56%), and showed evidence of plasma cells in 86 (90%). CSF flow cytometry was performed in 80 patients (47%), and showed a monoclonal plasma cell population in 73 (91%). The flow cytometry profile is shown in 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 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 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 (Figure 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 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 (Figure 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; Figure 1D).

In the univariate analysis, 1 or more lines of therapy for MM prior to CNS MM diagnosis vs. no previous therapy (Figure 2A), ISS staging (Figure 2B), and >1 FISH abnormality vs. 0–1 abnormalities (Figure 2C) were associated with a worse OS. The presence of a mass on MRI/CT was associated with a better OS (Figure 2D) when compared with the presence of leptomeningeal enhancement. Age, sex, 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 Table 3.

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 3 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; Figure 3A). In a subgroup sensitivity analysis, the increased score remained associated with shortened OS after removal of patients who were not treated (Figure 3B), in patients who received systemic therapy (Figure 3C), and in patients who did not receive systemic therapy (Figure 3D).

DISCUSSION

In the present study of 172 CNS MM cases, the risk of CNS involvement was not associated with sex, as CNS MM was found with similar incidence in men and women. 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 are more prone to develop lesions in CNS. This observation is consistent with other reports on CNS involvement in MM [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). Although in previously reported cases CNS involvement was also detected synchronically to primary MM, it is more often associated with more advanced stages of the disease (secondary CNS MM) [3,5–7]. However, the distribution of ISS stages in our cohort was relatively even without favoring more advanced stages, which suggests that development of CNS MM is not 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].

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]. The incidence of cytogenetic changes was not compared with any control group and we cannot conclude that any of changes makes the development of CNS MM more probable. However, the presence of adverse genetic abnormalities was associated with prognosis and it was incorporated into the proposed prognostic scoring system. 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 empirically [13]; also the vast majority (70%) of our patients who have been tested for this antigen showed its normal expression on plasma cells isolated from CSF.

Detection of CNS MM on the basis of imaging studies can be challenging. The lesions found within CNS may be heterogeneous, ranging from leptomeningeal infiltration to well-demarcated masses. The presence of mass or infiltration on imaging studies alone is insufficient for establishing the diagnosis of CNS MM due to high incidence of false positive and false negative results [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 was also associated with a false negative rate of 10% [6]. Therefore it is preferable to perform imaging, pathological and CSF examination concurrently. Presence of clonal plasma cells in CSF, or pathological evidence of soft tissue infiltration, should point towards the diagnosis of CNS MM. However, in daily clinical practice, it is not always possible to obtain specimen for histopathological assessment due to poor performance status, end-stage disease or patient’s refusal. Moreover, the presence of plasma cells in CSF does not constitute a diagnosis of CNS MM, unless monoclonal [18]. On the other hand, plasma cells can be absent in CSF from patients with parenchymal infiltration or isolated changes in the dura mater [19]. Therefore, the absence of plasma cells in CSF does not rule out the diagnosis of CNS MM. CSF cytology should be accompanied by flow cytometry, as polyclonal plasma

cells can be also found in other conditions [6]. Our study was retrospective and involved patients treated in different centers which did not follow the same diagnostic and treatment protocol and that's way only limited proportion of patients were evaluated with all mentioned diagnostic procedures, i.e. MRI or CT, pathological and CSF examination. On the other hand our data represents a real-life routine practice and shows that the diagnosis of CNS MM can be established 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, but compared the outcomes of patients subjected to chemotherapy and/or radiotherapy with the results of individuals who were left untreated or offered other treatment modalities (for example only steroids, intrathecal therapy or radiotherapy). 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 [4] and pomalidomide [16], can penetrate to CNS. One study demonstrated that administration of pomalidomide to a patient with CNS involvement resulted in disappearance of plasma 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, although experiences with this agent are limited to 2 published case reports and no strong recommendation on bendamustine can be made [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 to this date, did not prove to be efficient as monotherapy [28]. Although whole brain radiation is a therapeutic option in CNS MM, its practical application is limited due to toxicity. Localized metastases to CNS can also 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 (200 mg/m^2) prior to autologous HSCT [16,30]. Although there are few published reports documenting favorable effects of allogeneic HSCT in patients with CNS involvement, the graft-versus-myeloma effect is generally limited.

In our study, the patients treated only with intrathecal therapy or intrathecal therapy combined with radiotherapy had poor survival. It should be noted that only when combined with systemic therapy, intrathecal administration of cytotoxic agents enabled to prolong survival. Although the 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 constitutes 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 is poor and in our study we observed a 75% mortality within 2 years of diagnosis. This 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. Dr Paludo et al suggested that mSMART classification ingredients might play a role as prognostic factors in CNS MM patients [Paludo et al 3119 Myelomatous Involvement Of The Central Nervous System: Mayo Clinic Experience, ASH 2013]. 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 scoring system based on these two factors enabled us to stratify our patients in three groups. 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 was not necessarily 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, although highly desirable and needed, 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.

Authors

Artur Jurczyszyn[1], Norbert Grzasko[2], Alessandro Gozzetti[3], Jacek Czepiel[1], Alfonso Cerase[3], Vania Hungria[4], Edvan Crusoe[4], Ana Luiza Miranda Silva Diaz[4], Ravi Vij[5], Mark A. Fiala[5], Jo Caers[6], Leo Rasche[7], Ajay K. Nooka[8], Sagar Lonial[8], David H. Vesole[9], Sandhya Philip[9], Shane Gangatharan[10], Agnieszka Druzd-Sitek[11], Jan Walewski[11], Alessandro Corso[12], Federica Cocito[12], Marie-Christine M. Vekemans[13], Erden Atilla[14], Meral Beksac[14], Xavier Leleu[15], Julio Davila[16], Ashraf Badros[17], Ekta Aneja[18], Niels Abildgaard[19], Efstathios Kastritis[20], Dorotea Fantl[21],

Natalia Schutz[21], Tomas Pika[22], Aleksandra Butrym[23], Magdalena Olszewska-Szopa[23], Lidia Usnarska-Zubkiewicz[23], Saad Usmani[24], Hareth Nahi[25], Chor S Chim[26], Chaim Shustik[27], Krzysztof Madry[28], Suzanne Lentzsch[29], Alina Swiderska[30], Grzegorz Helbig[31], Renata Guzicka-Kazimierczak[32], Nikoletta Lendvai[33], Anders Waage[34], Kristian T. Andersen[35], Hirokazu Murakami[36], Sonja Zweegman[37], and Jorge J. Castillo[38]

Affiliations

[1]Jagiellonian University Medical College, Cracow, Poland [2]Medical University of Lublin, Department of Hematooncology and Bone Marrow Transplantation, Lublin, Poland; St. John's Cancer Center, Department of Hematology, Lublin, Poland [3]Azienda Ospedaliera Universitaria Senese, Siena, Italy [4]Santa Casa Medical School, Sao Paulo, Brazil [5]Washington University School of Medicine, St. Louis, Missouri, USA [6]Centre Hospitalier Universitaire de Liege, Liege, Belgium [7]University Hospital Wuerzburg, Wuerzburg, Germany [8]Winship Cancer Institute, Emory University, Atlanta, Georgia, USA [9]John Theurer Cancer Center at Hackensack UMC, New Jersey, USA [10]Fremantle Hospital, Fremantle, Australia [11]Maria Sklodowska-Curie Institute – Oncology Center, Warsaw, Poland [12]Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy [13]Cliniques Universitaires Saint-Luc, Brussels, Belgium [14]Ankara University Medical School, Ankara, Turkey [15]Hospital Huriez, Lille, France [16]Hospital Universitario de Salamanca, Salamanca, Spain [17]University of Maryland Medical Center, Baltimore, Maryland, USA [18]Weill Cornell Medical College, New York, New York, USA [19]Odense University Hospital, Odense, Denmark [20]National and Kapodistrian University of Athens, Athens, Greece [21]Hospital Italiano de Buenos Aires, Buenos Aires, Argentina [22]University Hospital Olomouc, Olomouc, Czech Republic [23]Wroclaw Medical University, Wroclaw, Poland [24]Levine Cancer Institute/Carolinas HealthCare System, Charlotte, NC, USA [25]Karolinska University Hospital, Stockholm, Sweden [26]Queen Mary Hospital, University of Hong Kong, Hong Kong [27]Royal Victoria Hospital, McGill University, Montreal, Canada [28]Medical University, Warsaw, Poland [29]Columbia University Medical Center, New York, New York, USA [30]Provincial Hospital, Zielona Gora, Poland [31]Silesian Medical University, Katowice, Poland [32]Pomeranian Medical University, Szczecin, Poland [33]Memorial Sloan-Kettering Cancer Center, New York, New York, USA [34]Norwegian University of Science and Technology, Trondheim, Norway [35]Vejle Hospital, Vejle, Denmark [36]Gunma University Graduate School of Health Sciences, Gunma, Japan [37]VU University Medical Center, Amsterdam, The Netherlands [38]Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA

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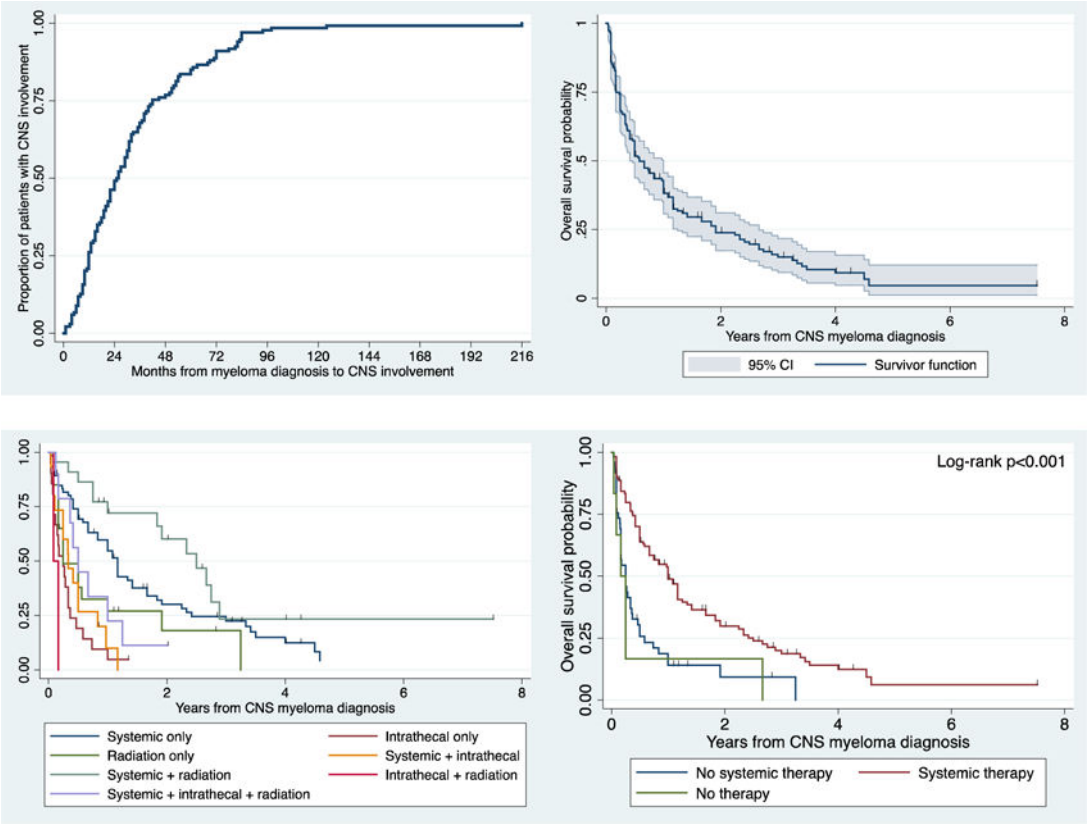

Figure 1.

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).

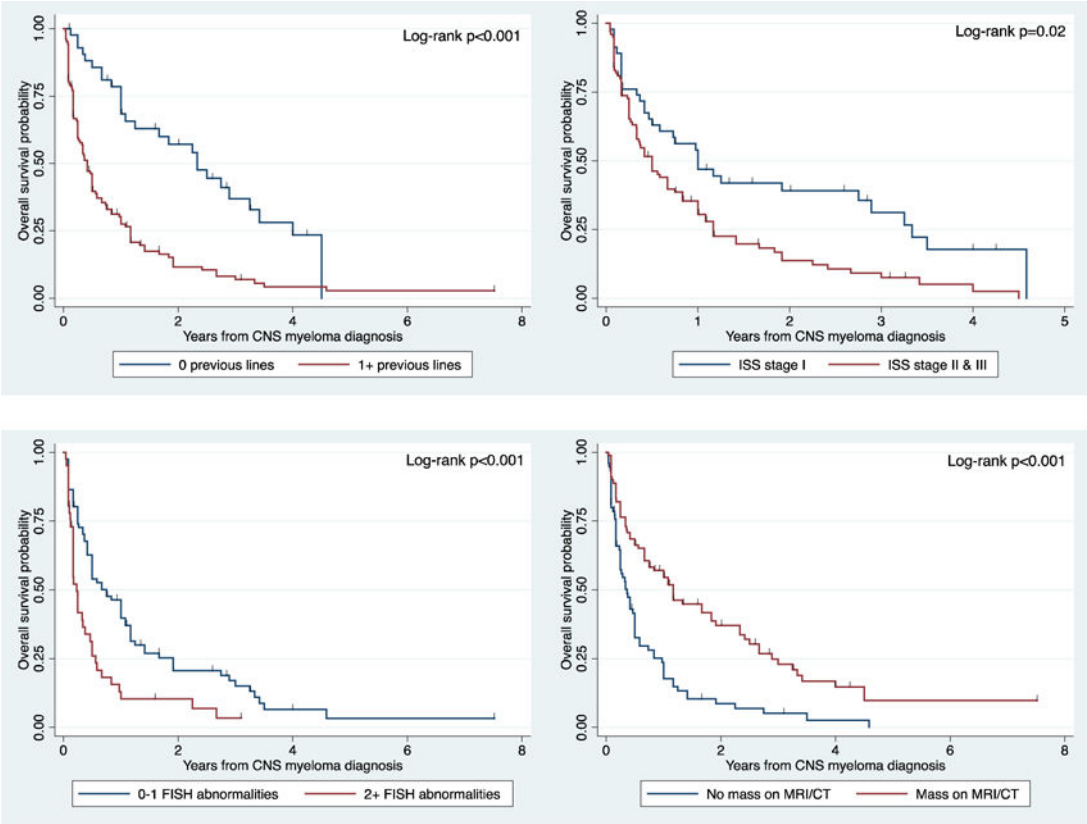

Figure 2.

OS estimates in patients with CNS myeloma, according to previous lines of therapy (A), ISS stage (B), number of FISH abnormalities (C), and presence of mass on MRI/CT (D).

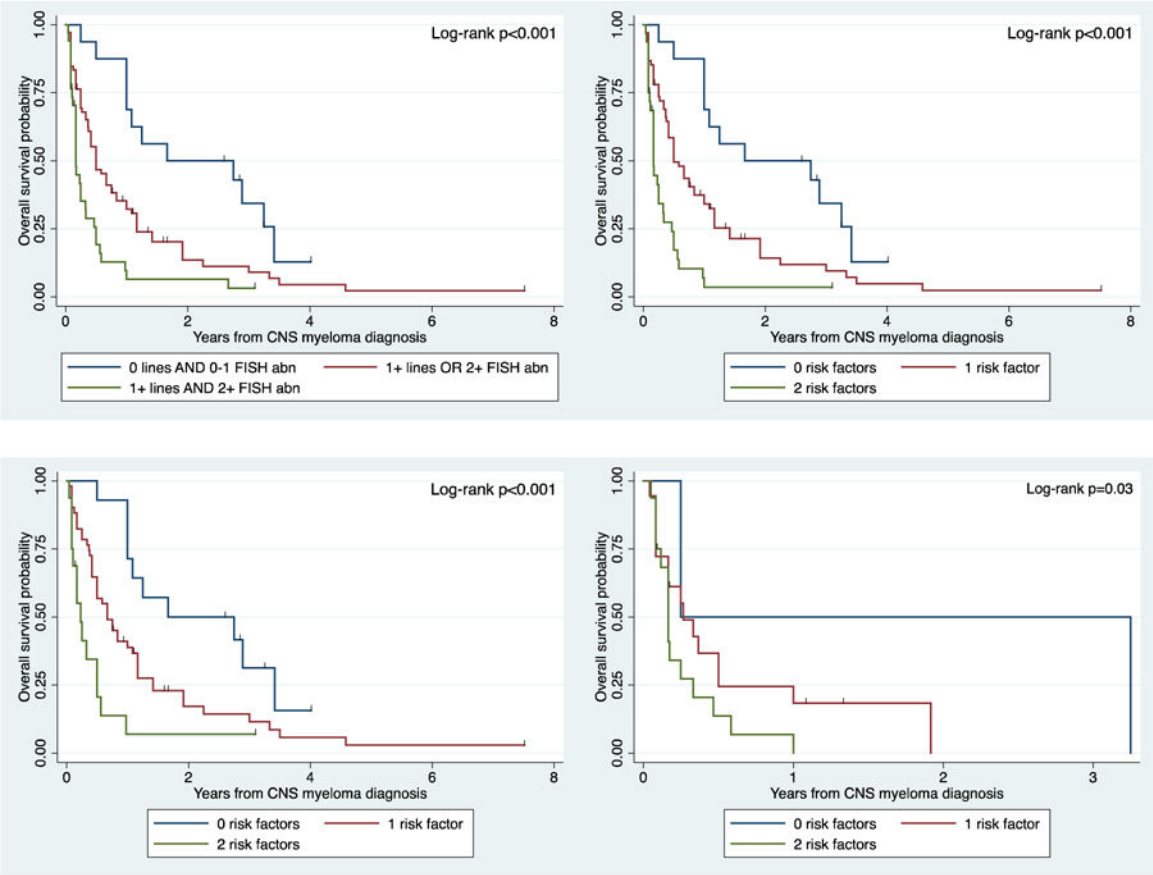

Figure 3.

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).

Table 1

Selected clinical characteristics of patients with CNS myeloma

Characteristic	N/median (%/range)
Age, in years (n=171)	
At myeloma diagnosis	53 (31–82)
At CNS myeloma diagnosis	56 (33–82)
Sex (n=171)	
Male	94 (55%)
Female	77 (45%)
Previous lines of myeloma therapy (n=172)	
0 previous lines	43 (25%)
1–2 previous lines	63 (37%)
>2 previous lines	66 (38%)
Heavy chain isotype (n=166)	
IgG	83 (50%)
IgA	45 (27%)
IgD	4 (2%)
Biclonal	2 (1%)
No heavy chain	32 (19%)
Light chain isotype (n=172)	
Kappa	89 (52%)
Lambda	73 (42%)
No light chain	1 (0.6%)
Biclonal	9 (5%)
LDH levels (n=88)	
Normal	47 (53%)
Elevated	41 (47%)
ISS stage (n=148)	
Stage I	47 (32%)
Stage II	61 (41%)
Stage III	40 (27%)
Symptoms at presentation (n=146)	
Visual changes	52 (36%)
Radiculopathy	40 (27%)
Headache	37 (25%)
Change in mental status	31 (21%)
Peripheral neuropathy	13 (9%)
Dizziness	10 (7%)
Seizures	9 (6%)
Auditory changes	1 (1%)

Characteristic	N/median (%/range)
FISH abnormalities	
Del13q	48/122 (39%)
Del17p	28/122 (23%)
t(4;14)	15/122 (12%)
t(11;14)	9/122 (7%)
Number of FISH abnormalities	
No abnormalities	45/122 (37%)
1 abnormality	36/122 (30%)
2 abnormalities	23/122 (19%)
>2 abnormalities	18/122 (15%)
CSF flow cytometry profile	
CD45	18/34 (53%)
CD19	3/34 (9%)
CD20	3/27 (11%)
CD4	0/5 (0%)
CD8	0/6 (0%)
CD56	35/50 (70%)
CD38	62/65 (95%)
CD138	31/33 (94%)

CNS: central nervous system; Ig: immunoglobulin; ISS: International Staging System; LDH: lactate dehydrogenase

Table 2

Frontline therapies and causes of death in CNS myeloma patients

Initial therapy (n=166)	**N (%)**
Systemic therapy only	69 (40%)
Systemic + radiotherapy	22 (13%)
Intrathecal therapy only	21 (12%)
Radiotherapy only	20 (12%)
Systemic + intrathecal therapy	16 (9%)
Systemic + intrathecal + radiotherapy	10 (6%)
Steroids only	5 (3%)
Intrathecal + radiotherapy	2 (1%)
Resection + radiotherapy	1 (1%)
Systemic therapy (n=117)	
Chemotherapy + proteasome inhibitors	36 (23%)
Chemotherapy	27 (18%)
Chemotherapy + IMIDs	19 (12%)
IMIDs	14 (9%)
Proteasome inhibitors + IMIDs	12 (8%)
Chemotherapy + proteasome inhibitors + IMIDs	5 (3%)
Proteasome inhibitors	3 (2%)
Other	1 (1%)
Intrathecal therapy (n=49)	
Methotrexate + cytarabine	21 (43%)
Methotrexate	7 (14%)
Cytarabine	3 (6%)
Thiotepa	2 (4%)
Unknown	16 (33%)
Causes of death (n=139)	
Disease progression	120 (86%)
Infection	13 (9%)
Bleeding	2 (1%)
Stroke	1 (1%)
Acute myeloid leukemia	1 (1%)
Congestive heart failure	1 (1%)
Multiorgan failure	1 (1%)

IMIDs: immunomodulators

Table 3

Univariate and multivariate analysis for overall survival in patients with CNS myeloma

Factor	Median OS (months)	Univariate		Multivariate	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Age					
At myeloma diagnosis	–	1.00 (0.98–1.01)	0.90		
At CNS myeloma diagnosis	–	1.00 (0.99–1.02)	0.65		
Sex					
Female	6.7 months	1.00			
Male	6 months	1.19 (0.84–1.67)	0.33		
Previous lines of therapy					
No previous	12 months	1.00		1.00	
1+ previous line	4.4 months	2.91 (1.89–4.47)	<0.001	2.22 (1.27–3.86)	0.005
ISS staging					
ISS stage I	12 months	1.00		1.00	
ISS stage II–III	5 months	1.88 (1.24–2.85)	0.003	1.63 (0.85–2.17)	0.19
LDH at CNS myeloma diagnosis*					
Normal	10 months	1.00			
Elevated	3.2 months	2.55 (1.56–4.19)	<0.001		
Heavy chain isotype					
IgG	7 months	1.00			
IgA	7 months	0.98 (0.65–1.46)	0.91		
IgD	2 months	1.96 (0.71–5.41)	0.19		
Non-secretory	8 months	0.93 (0.58–1.48)	0.76		
Biclonal	3 months	1.19 (0.29–4.86)	0.81		
Light chain isotype					
Kappa	6 months	1.00			
Lambda	6 months	1.08 (0.76–1.52)	0.67		
No light chain	13 months	0.70 (0.31–1.63)	0.41		
Biclonal	3 months	3.62 (0.49–26.5)	0.21		

Factor	Median OS (months)	Univariate		Multivariate	
		HR (95% CI)	p-value	HR (95% CI)	p-value
FISH abnormalities					
0–1 abnormalities	8 months	1.00		1.00	
>1 abnormality	2.8 months	2.09 (1.38–3.16)	<0.001	2.26 (1.41–3.61)	0.001
Leptomeningeal enhancement					
Absent	8 months	1.00			
Present	6 months	1.20 (0.85–1.70)	0.30		
Mass					
Absent	4 months	1.00		1.00	
Present	13 months	0.44 (0.31–0.62)	<0.001	0.88 (0.57–1.36)	0.57

OS: overall survival; HR: hazard ratio; CI: confidence interval; CNS: central nervous system; ISS: International Staging System; LDH: lactate dehydrogenase; Ig: immunoglobulin; FISH: fluorescence in situ hybridization