Clinical Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2016, Vol. 44(6) 1462–1473

DOI: 10.1177/0300060516664820
imr.sagepub.com
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Clinical analysis of 40 multiple myeloma patients with extramedullary plasmacytoma of the head

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Abstract

Objectives: To investigate the clinical characteristics, survival and prognosis of patients with multiple myeloma (MM) and head extramedullary plasmacytoma (EMP).

Methods: Forty MM patients were enrolled in the study (18 men, 22 women; median age, 55 years).

Results: Median overall survival (OS) and progression-free survival (PFS) were 24 (5–78) months and 17 (2–36) months, respectively. The 2-, 3- and 5-year OS rates were 51%, 20% and 7%, respectively. The 2-year PFS was 15%. Median OS and PFS in patients administered velcade were 26 (18–50) and 22.5 (5–78) months, compared with 20 (10–30) and 13.5 (2–36) months in patients without velcade, respectively. Median OS was 23.5 (5–50) months in patients with EMP at MM diagnosis ($n = 25$) and 36 (22–78) months in patients with head EMP diagnosed during the disease course ($n = 15$). Sixteen MM patients had EMP invasion of the head only and 24 had invasion at multiple sites. Median OS was 25 (22–78) months in patients with EMP of the head only and 22 (5–78) months in patients with EMP invasion at multiple sites.

Conclusion: MM patients with head EMP show a more aggressive disease course and shorter OS and PFS. The prognosis of these patients is poor, especially in patients with head EMP at MM diagnosis, though combined chemotherapy and radiotherapy may prolong survival.

Keywords

Head extramedullary plasmacytoma, multiple myeloma, prognosis, survival

Date received: 18 May 2016; accepted: 27 July 2016

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Introduction

Multiple myeloma (MM) is a malignant lymphoproliferative B-cell disease characterized by the accumulation of monoclonal plasma cells in the bone marrow. Plasma cells are usually restricted to the bone marrow, but may also migrate into perivascular spaces and direct extensions from bony lesions. Extramedullary plasmacytoma (EMP) is a rare monoclonal plasmacytic proliferation occurring in extraskeletal sites, which may occur in patients with MM, either at diagnosis or during the course of the disease.[1] The most common sites of EMP are the nasopharynx, larynx and upper respiratory tract (82.2%).[2] Disseminated MM also includes invasion of the gastrointestinal tract,[3] pleura, testis,[4] skin,[5] liver[6] and endocrine glands. MM with central nervous system (CNS) EMP has been reported to be rare and associated with specific features.[7,8] The present study analysed the clinical characteristics and survival of 40 MM patients with head EMP.

Materials and methods

Patients

Among a series of 425 symptomatic patients with MM at Beijing Chao Yang Hospital (Western Area of Beijing Chao Yang Hospital) and the PLA Rocket Forces General Hospital, 40 (9.4%) patients with head EMP were included in this study from June 2005 to December 2014. There were 18 men and 22 women with a median age of 55 years (range 28–79 years). The patients were diagnosed with MM according to MM diagnostic criteria, and staged according to the International Staging System (ISS) and Duric–Salmon staging system. Patients with EMP were examined using magnetic resonance imaging or computerized tomography, or diagnosed by pathological criteria based on treatment effect, according to the International Myeloma Working Group (IMWG). Karyotype analysis was carried out using G-banding techniques in 10 patients and using fluorescence in situ hybridization (FISH) in five patients.

Methods

Patients were divided into two groups for analysis of progression-free survival (PFS) and overall survival (OS): a velcade group (25 cases) and a without-velcade group (15 cases). The velcade group was treated with one of the following: velcade + dexamethasone (velcade 1.3 mg/m^2 on days (d)1, 4, 8, and 11; dexamethasone 20 mg d1, 4, 8, and 11), velcade + ifosfamide + dexamethasone (velcade 1.3 mg/m^2 d1, 4, 8, and 11; ifosfamide 0.5 g d1–4; dexamethasone 20 mg d1, 4, 8, and 11), or velcade + pirarubicin + dexamethasone (velcade 1.3 mg/m^2 d1, 4, 8, and 11; pirarubicin 10 mg d1–4; dexamethasone 20 mg d1, 4, 8, and 11). Some patients chose conditional chemotherapy (without-velcade group) for financial reasons: MP (melphalan 8 mg/m^2/d oral, d1–4; prednisone 60 mg/m^2/d oral, d1–4), M2 (vinblastine 1.2 mg/m^2/d, d1; Me-CCUN 20 mg/m^2/d, d1; melphalan 8 mg/m^2/d oral, d1–4; cyclophosphamide 400 mg/m^2/d, d1; prednisone 60 mg/m^2/d oral, d1–14), VAD (vinblastine 0.4 mg d1–4; epirubicin 10 mg d1–4; dexamethasone 20 mg d1–4, 9–12) or CTD (ifosfamide 0.5 g d1–4; dexamethasone 20 mg d1–4; thalidomide 100 mg oral each night). Four patients received radiotherapy and two patients received autologous stem cell transplantation in the velcade group.

In this analysis, the diagnosis of MM was defined according to the criteria of the IMWG[9] and responses to treatment, including complete and partial remission (CR and PR) and progressive disease (PD) status, were defined according to the Bladè criteria.[10]

Statistical analyses

The probabilities of PFS and OS were estimated using the Kaplan–Meier method.

The durations of PFS and OS in the different groups were compared using log-rank tests. PFS was defined as the time from CR to relapse and progression, death from any cause, or censoring of patient data. OS was defined as the time from registration to death or censoring of patient data. Cox regression analyses of OS were performed for multivariate prognostic factors.

Ethics statement

This study was approved by the Ethics Committee of Beijing Chao Yang Hospital, Capital Medical University and PLA Rocket Forces General Hospital, which waived the requirement for obtaining patient informed consent because of the anonymity of the patient data. All aspects of the study complied with the Declaration of Helsinki.

Results

Basic clinical characteristics of the patients

Forty patients were enrolled in this study, including 22 IgG (55%), seven IgA (17.5%) and 11 light chain (27.5%) MM patients. The basic characteristics of the patients did not differ significantly between the two groups (Table 1). All patients were stage III (DS), including 32 cases of IIIa (80%) and eight cases of IIIb (20%). Eight (20%) patients had stage II and 32 (80%) patients had stage III according to ISS staging. The first symptom was bone pain in 11 cases (27.5%), diplopia in eight cases (20%), weakness in three cases (7.5%) and identification of a mass in 18 cases (45%). Among patients with disease progression, 15 (37.5%) patients had pleural effusion, three (7.5%) had polyserous effusions, and eight (20%) had splenomegaly. One patient had paraplegia at initial diagnosis and four patients had paraplegia after disease progression. Among these 40 patients, 24 had EMP invasion at multiple sites and 16 had EMP of the head alone (Figures 1 and 2). The most common location of invasion was the head, including the retrobulbar tissue of the eyeball (14 cases), sphenoid sinus and ethmoidal cells (12 cases), mandible (11 cases), skull (10 cases), and the CNS (five cases). EMP of the head in MM patients usually involves more than one site. In addition to head EMP, EMP also occurred in soft tissue in the chest wall in 16 patients, the spinal canal in five, the ovary in two, breast in four, tonsils in one, liver in two, abdominal cavity in five, mediastinum in three, pancreas in two, kidney in one, and lung in one.

Among 10 patients karyotyped by G-banding patients, the karyotype was normal in eight patients and two patients had complex chromosome abnormalities. Two patients had 1q21 amplification, two patients had t(14;16) and one patient was normal, as measured by FISH.

Survival

Survival following treatment. Twenty patients had died by the end of the follow-up on December 31, 2014. The median OS was 24 (5–78) months and the median PFS was 17 (2–36) months. The 2-, 3- and 5-year OS rates were 51%, 20% and 7%, respectively. The 2-year PFS was 15% (Figures 3 and 4). The median OS was 26 (18–50) months in the velcade group and 22.5 (5–78) months in the without-velcade group, and the median PFS was 20 (10–30) months in the velcade group and 13.5 (2–36) months in the without-velcade group. There were no significant differences in OS and PFS between these two groups ($P = 0.293$ and $P = 0.123$) (Figures 5 and 6). Four patients received radiotherapy and survived longer than 3 years. One patient received an intrathecal injection of dexamethasone (10 mg) plus cytarabine (50 mg) and velcade combination chemotherapy, followed by radiotherapy, and survived more than 18 months after the development of head EMP. Among

Table 1. Characteristics of 40 MM patients with head extramedullary plasmacytoma treated with and without velcade.

Characteristic	With-velcade group ($n=25$)	Without-velcade group ($n=15$)	Total ($n=40$)
Age, years	59(28–86)	54(28–78)	55(28–79)
Sex, male/female	9/9	9/13	18/22
Albumin, g/l	32.3(21.3–39.4)	29.8(18.9–40.1)	31.5(18.9–40.1)
Leucocytes, $\times 10^9$/l	4.9(1.8–10.1)	4.3(3.2–7.6)	4.8(1.8–10.1)
Haemoglobin, g/l	101(85–132)	83.5(46–153)	100(46–153)
Platelets, $\times 10^9$/l	221(88–280)	175(44–300)	212(44–300)
C-reactive protein, mg/l	5(2–97)	5(5–120)	5(2–120)
Sedimentation, mm/h	56(5–120)	90(22–140)	58(5–140)
β2-microglobulin, mg/l	3.75(1.67–14.48)	6.65(2.27–17.78)	4.25(1.67–17.78)
Bone marrow plasmacytosis, %	30.5(10.5–48)	43.5(21.5–93.5)	43(10.5–93.5)
Lactate dehydrogenase, U/l	371(91–1908)	160(90.6–382)	198(90.6–1908)
Uric acid, μmol/l	308.8(192–661.6)	424(237.3–803.3)	333.1(192–803.3)
Serum creatinine, μmol/l	134.3(46.7–446.9)	77(45.9–301.3)	87.5(45.9–446.9)
Calcium	2.27(1.93–3.18)	2.38(2.03–2.90)	2.29(1.93–3.18)
Site of EMP	Head only ($n=10$)	Head only($n=6$)	$n=16$
	Retrobulbar tissue of the eyeball($n=9$)	Retrobulbar tissue of the eyeball($n=5$)	$n=14$
	Sphenoid sinus and ethmoidal cells($n=6$)	Sphenoid sinus and ethmoidal cells($n=6$)	$n=12$
	Mandible($n=8$)	Mandible($n=3$)	$n=11$
	Skull ($n=5$)	Skull ($n=5$)	$n=10$
	Central nervous system($n=4$)	Central nervous system ($n=1$)	$n=5$
	Head and other site($n=15$)	Head and other site($n=9$)	$n=24$
	Chest wall($n=8$)	Chest wall($n=8$)	$n=16$
	Spinal canal($n=4$)	Spinal canal($n=1$)	$n=5$
	Ovary($n=2$)	Ovary($n=0$)	$n=2$
	Breast($n=3$)	Breast($n=1$)	$n=4$
	Tonsils($n=1$)	Tonsils($n=0$)	$n=1$
	Liver($n=2$)	Liver($n=0$)	$n=2$
	Abdominal cavity($n=4$)	Abdominal cavity($n=1$)	$n=5$
	Mediastinum($n=2$)	Mediastinum($n=1$)	$n=3$
	Pancreas($n=2$)	Pancreas($n=0$)	$n=2$
	Kidney($n=1$)	Kidney($n=0$)	$n=1$
	Lung($n=1$)	Lung($n=0$)	$n=1$

the 25 patients in the velcade group, eight had CR, 14 had PR, and three had PD, while among the 15 patients in the without-velcade group, four had CR, seven had PR, and four had PD.

Survival of patients with EMP. Fifteen patients developed head EMP during the course of MM and 25 patients had head EMP at MM diagnosis. The median OS rates were 36 (22–78) months and 23.5 (5–50) months in

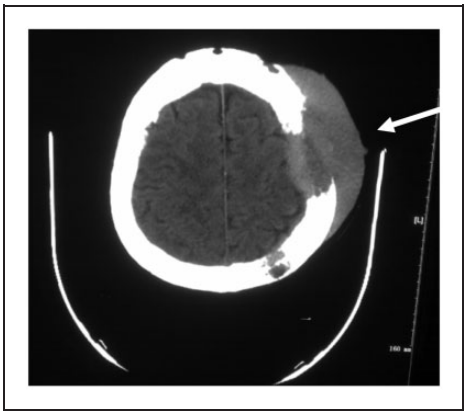

Figure 1. MM patient with EMP invasion of the skull.

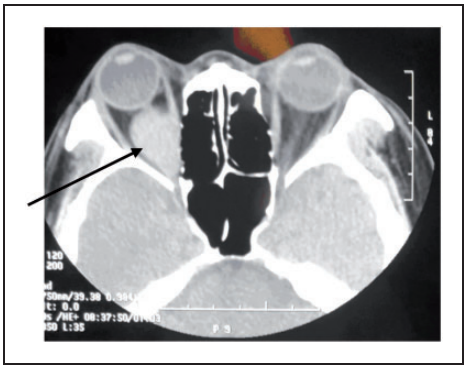

Figure 2. MM patient with EMP invasion of retrobulbar tissue of the eyeball.

MM patients with head EMP during disease progression and at diagnosis, respectively. OS was significantly higher in patients with EMP during disease progression ($P = 0.014$) (Figure 7). The median survival time from the development of head EMP to death was 6 (3–18) months in patients who developed head EMP during the disease course. The median PFS rates were 24 (7–36) months and 15 (2–30) months in patients who developed head EMP during the disease course and those with head EMP at diagnosis, respectively There was no significant difference in PFS between the two groups ($P = 0.082$) (Figure 8).

Survival of patients with EMP at different invasion sites. Fourteen patients had EMP invasion of the retrobulbar tissue of the eyeball, which caused eyeball extrusion or diplopia. The median OS rates were 31 (21–50) months in MM patients without EMP invasion of retrobulbar tissue ($n = 26$) and 22.5 (5–78) months in those with retrobulbar invasion ($n = 14$), with no significant difference between the two groups ($P = 0.191$).

Sixteen patients had EMP invasion of the head alone and 24 patients had EMP invasion at multiple sites. The median OS rates were 25 (22–78) months in patients with invasion of the head alone and 22 (5–78) months in those with invasion at multiple sites. OS was significantly higher in patients with head invasion alone ($P = 0.032$) (Figure 9).

Prognosis

Cox regression was performed to identify potential independent prognostic factors for OS. The following factors were evaluated as prognostic variables for OS: sex, age, initial peripheral leucocyte count, haemoglobin, platelets, C-reactive protein, erythrocyte sedimentation, β2-microglobulin, lactate dehydrogenase, albumin, uric acid, bone marrow plasmacytosis, serum creatinine, calcium, treatment and EMP of the head at diagnosis or during the disease course. Analysis showed that only EMP of the head at MM diagnosis was a significant prognostic factor for OS.

Discussion

Multiple myeloma accounts for 10% of all haematological malignancies, with an incidence of five cases per 100 000/year and a median age at onset of 65–70 years, with a slight male predominance. EMPs occur in 7%–17% of patients at MM diagnosis and

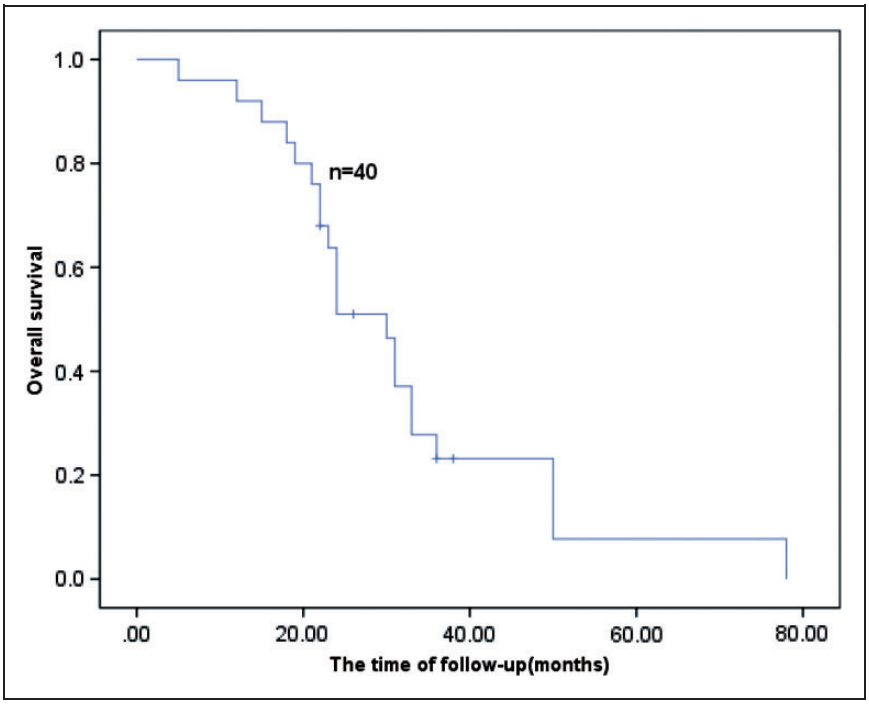

Figure 3. OS of MM patients with head extramedullary plasmacytoma.

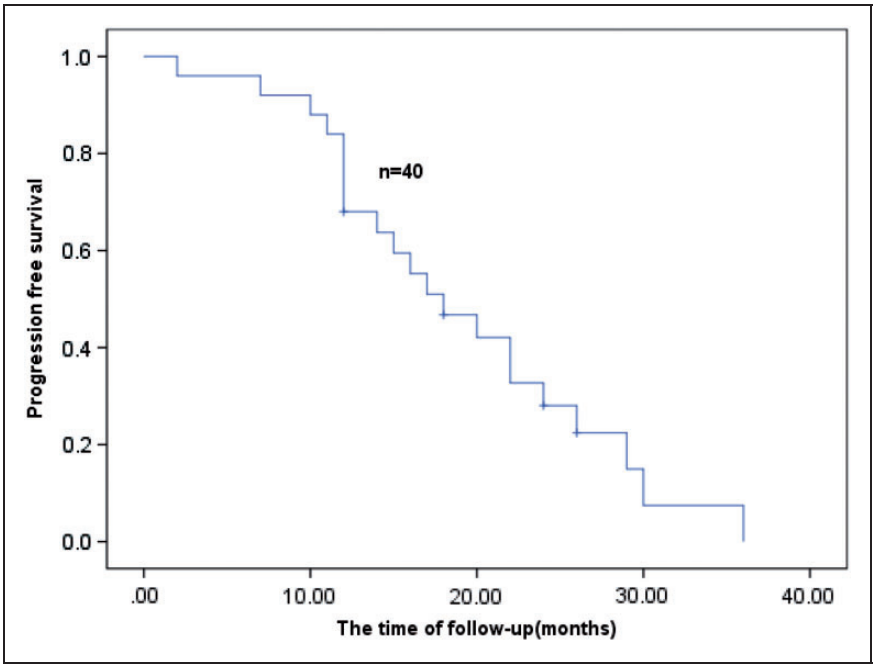

Figure 4. PFS of MM patients with head extramedullary plasmacytoma.

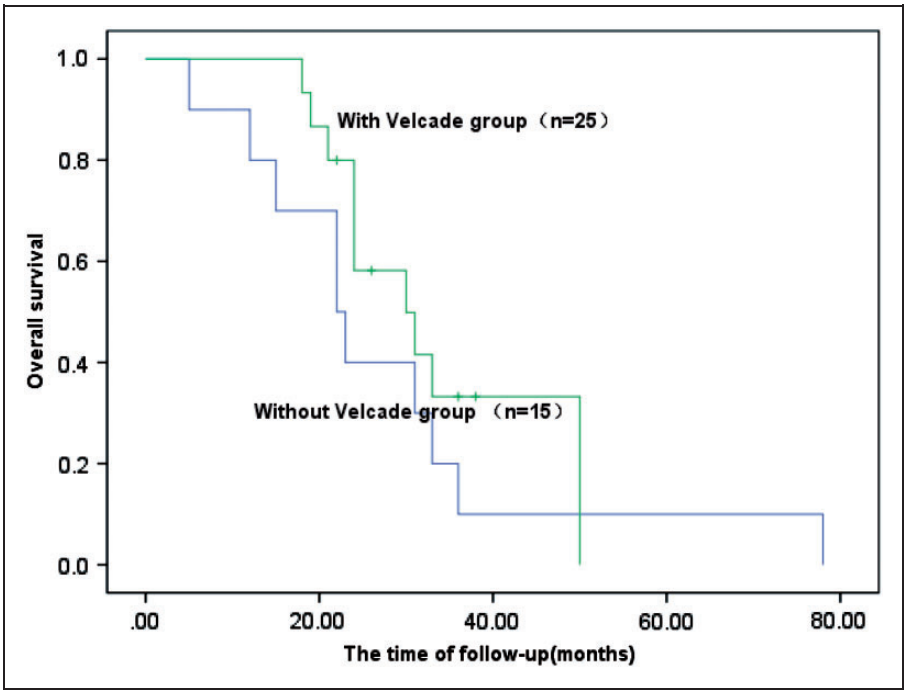

Figure 5. OS of MM patients with head extramedullary plasmacytoma treated with and without velcade. There was no significant difference between the groups.

in 6%–20% during the disease course.[11,12] In this study, the incidence of head EMP among 425 MM patients was 9.4% over the past 10 years. In a previous study of 3600 MM patients in the Taiwan National Cancer Registry, the prevalence of EMP was significantly higher in patients aged < 55 years.[13] The median age of MM patients with head EMP in the present study was 55 years, which was similar to that in the above study, but lower than in other MM populations. Schluterman et al.[14] reported on 23 MM patients with EMP invasion of the CNS, including 11 patients with IgG, seven with IgA, three with light chain, one with non-secretory and one with biclonal disease. In the present study, 22 patients had IgG, 11 had light chain and seven had IgA disease. Damaj et al.[15] reported no associations between the laboratory characteristics of MM at diagnosis and the incidence of EMP. In accord with Schluterman et al. and Damaj et al. above, this study also found no association between head EMP and MM subtype.

EMP comprises 3%–5% of all plasma cell neoplasms and accounts for less than 1% of all malignant head and neck tumors.[16,17] The upper airway is involved in 80% of cases. In this study, the most common locations of head EMP invasion were the retrobulbar tissue of the eyeball (14 cases), sphenoid sinus and ethmoidal cells (12 cases), mandible (11 cases), skull (10 cases), and CNS (five cases), indicating that the tissue surrounding the eyeball was the preferred location for head EMP. The median OS in MM patients without EMP invasion of retrobulbar tissue was longer than that in those with retrobulbar invasion (31 versus 22.5 months). However, there was no significant difference in OS between the

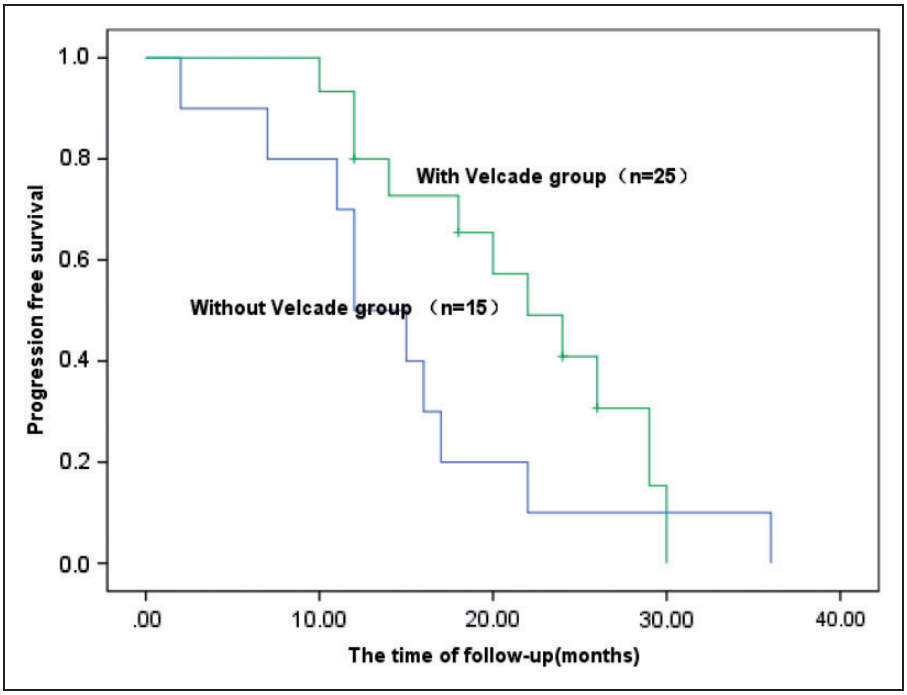

Figure 6. PFS of MM patients with head extramedullary plasmacytoma treated with and without velcade. There was no significant difference between the groups.

two groups ($P = 0.191$). These results suggest that patients who present with an extruding eyeball or diplopia and headache should be seen by an ear, nose and throat specialist. Suspected head EMP must be confirmed by magnetic resonance imaging or computerized tomography scanning as early as possible.

Published data show that OS is generally short in patients with EMP. Reports from China found a median OS in patients with EMP of 28 months,[1] while Varettoni et al.[12] reported median OS and PFS in MM patients with EMP of 36 months and 18 months, respectively. The presence of EMP at any time during the disease course was associated with significantly shorter OS and PFS. Schluterman et al.[14] reported a median OS from diagnosis of LMM of 3 months (range 0.1–25) in 23 MM patients with EMP invasion of the CNS. In our study, 20 patients had died by the end of the follow-up period, with a median OS of 24 (5–78) months and median PFS of 17 (2–36) months and 2-, 3- and 5-year OS rates of 51%, 20% and 7%, respectively. The 2-year PFS was 15%. The median OS and PFS rates in MM patients with head EMP were lower than in other EMP patients.

Although MM remains an incurable disease, considerable improvements in survival have been achieved as a result of the introduction of autologous stem cell transplantation and new drugs. However, EMP remains a complication associated with poor survival in MM patients. Gozzetti et al.[18] studied 50 patients with extramedullary intracranial localization of MM. New therapies were used in 35 patients, whereas 15 patients received traditional treatment.

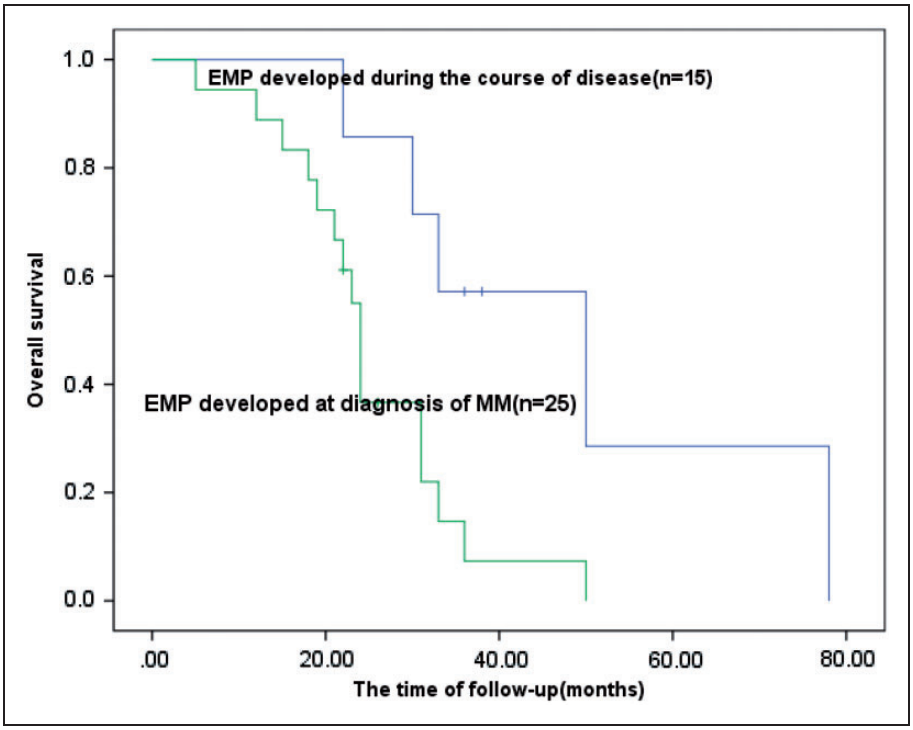

Figure 7. OS of MM patients who developed EMP during the disease course and those who had EMP at MM diagnosis ($P = 0.014$).

Twenty-five of the 50 patients achieved CR or very good PR, and OS was 25 months for patients treated with new agents versus 8 months with traditional agents. In our study, the OS and PFS were longer in patients treated with combination chemotherapy including velcade, compared with patients treated with traditional chemotherapy (26 versus 22.5 months and 20 versus 13.5 months, respectively). However, there were no significant differences in OS and PFS between the two groups. The reason why velcade did not increase survival in this study may be associated with the results of studies conducted in non-human primates, which indicated that velcade does not penetrate into the CNS or various regions of the eye.[19] Chen et al.[8] reported the outcomes of 37 patients with EMP invasion of the CNS. Intrathecal (IT) chemotherapy was administered to 81% of patients, cranial and/or spinal irradiation to 78%, and various systemic therapies (immunomodulatory agents 51%, cisplatin-based [DPACE; cisplatin, doxorubicin, cyclophosphamide, etoposide] 27%, bortezomib 19%, alkylators 11%, dexamethasone alone 8%, auto-transplant 5%). Median survival in patients with CNS disease was only 4.6 months, though nine patients had prolonged survival (median 17.1 months). In our study, four patients received radiotherapy and survived longer than 3 years. One patient received IT dexamethasone (10 mg), cytarabine (50 mg) and velcade combination chemotherapy, followed by radiotherapy, and was still alive more than 18 months after the development of head EM. These results are similar

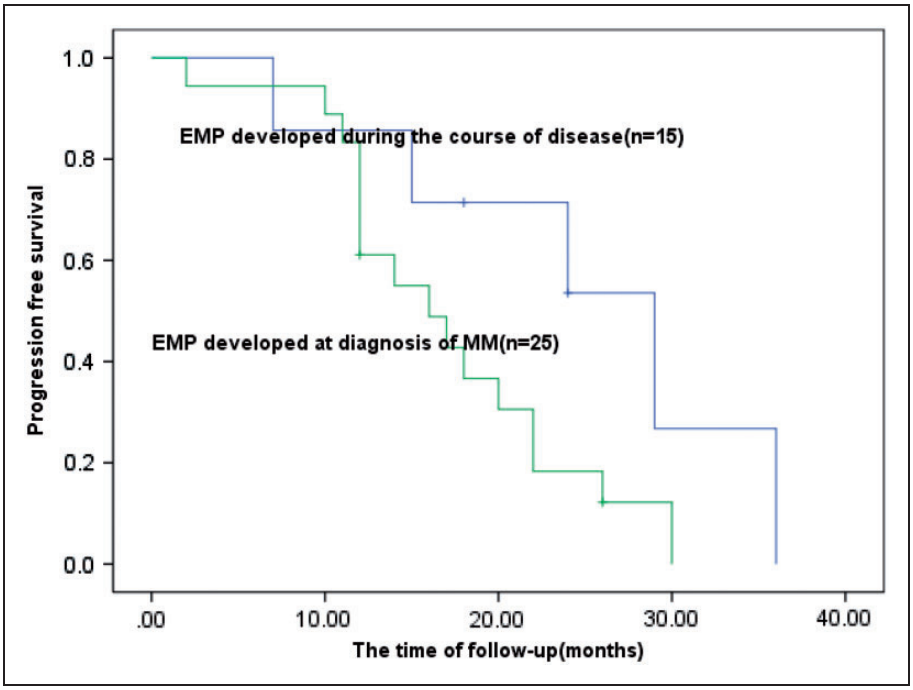

Figure 8. PFS of MM patients who developed EMP during the disease course and those who had EMP at MM diagnosis. There was no significant difference between the groups.

to those of Chen et al., and suggest that long-term survival may be achieved by using a combination of chemotherapy with new drugs and radiation or IT chemotherapy.

The OS of patients with head EMP at diagnosis was shorter than that of patients who developed EMP during the disease course. Log-rank univariate analysis showed that head EMP at MM diagnosis was the only significant prognostic factor for OS. Chen et al.[1] also reported poor prognosis in patients diagnosed with concurrent MM and EMP.

As noted above, our study found that the OS of MM patients with EMP at diagnosis was shorter than that of patients with EMP during the course of disease, indicating that EMP was a poor prognostic factor in MM patients. Weinstock et al. reported that the median OS from the time of myeloma diagnosis was 4.1 years (95% confidence interval [CI] 3.1–5.1) and the median OS from time of EMD diagnosis was 1.3 years (95% CI 0.8–2.3). With respect to prognosis, Deng et al. reported that EMD was an independent adverse prognostic factor according to multivariate analysis. The OS rates of patients with and without EMD at diagnosis were 16.5 and 40 months, respectively ($P < .001$), and the times to disease progression of the two groups were 11.5 and 25 months, respectively ($P < .001$). MM patients with EMD at the time of diagnosis also showed remarkably greater prevalence of p53 deletion according to FISH analysis, and higher lactate dehydrogenase levels.

In summary, MM patients with head EMP have a more aggressive disease course and shorter OS and PFS. The prognosis of these patients is very poor, especially in

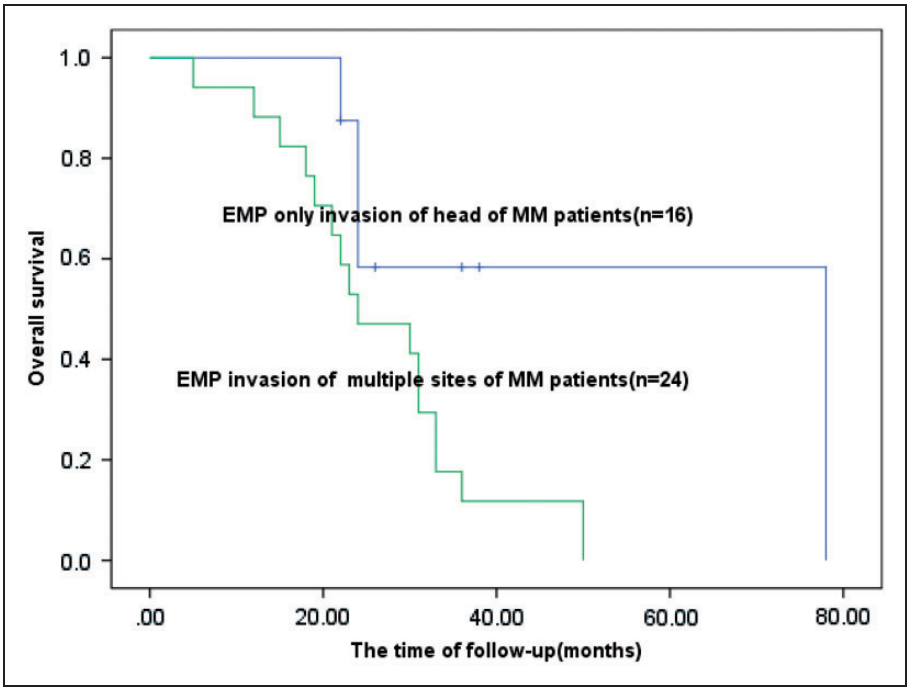

Figure 9. OS of MM patients who had EMP invasion of the head only and those who had EMP invasion at multiple sites ($P = 0.032$).

patients who present with head EMP at MM diagnosis. Combination chemotherapy including velcade and radiotherapy may prolong survival, but newer treatments and clinical trials are urgently needed.

Author contributions

Jia-jia Zhang, Na An and Man Shen collected and assembled and analysed the data, drafted the article, and critically revised and approved the manuscript. Xin Li contributed to the study concept and design and interpretation of the data, and provided statistical expertise and critical revision, and approved the manuscript.

Acknowledgements

The authors thank Wan-jun Sun for helpful suggestions and Zhong-xia Huang for stimulating discussions.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research had received support by the Science and technology plan project of Beijing, the number of project is Z161100000516231.

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