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Clinical Research
Clinical outcome of Extramedullary plasmacytomas in multiple myeloma

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Abstract: ***This study is retrospective investigation of extramedullary plasmacytomas(EMPs) in patients with multiple myeloma (MM) . The main purpose is to discuss the clinical characteristics and treatment.*** *Method:**We studied 79 patients of EMP in MM, and collected the clinical characteristics, laboratory features, treatment, and prognosis of extramedullary plasmacytoma(EMP) in patients with multiple myeloma(MM). Pataints were divided into two groups: group 1 included 32 patients who developed EMP during the course of MM; group 2 included 47 patients who had EMP at the time of MM diagnosis.*** *Result:* ***The median patient age was 56.2 years, with a male/female ratio of 45:34. MM cells can invade all parts of the body.*** *The most common sites for EMP were soft tissues(50 patients), spinal canal (36 patients). The median survival duration of the two groups was 33.6 months (range: 8–96 months) and 21 months (range: 1–52 months) respectively.**Especially for 2 groups,is less than the average survival time 3-5 years with the comparison to the patients who were not combinated with EMP.*** *Conclusion:**The occurrence of EMPs in patients with MM is associated with poor outcomes.***

Keywords: multiple myeloma, extramedullary plasmacytoma, chemotherapy.

1. Introduction

Multiple myeloma (MM) is a clonal B-cell malignancy of terminally differentiated plasma cells and the second most common cancer of blood-forming cells. Because myeloma is most commonly diagnosed in patients who are over 60 years of age, its incidence has increased in recent years as the population ages. EMP refers to a malignant plasma cell tumor growing outside bone and bone marrow.

Many patients develop soft-tissue EMPs, which may constitute the most prominent clinical feature[1,2-9]. In recent years, with the extension of survival times and advances in testing methods, the incidence of EMP has increased markedly.The appearance on imaging of EMP is diversiform, and the condition is easily misdiagnosed.To improve the accuracy of EMP diagnosis and survival, we studied the frequency, clinical features, laboratory findings, and response to treatment of EMP in patients with MM.

2. Patients and Methods

Patients

We searched the Department of Lymphoma/Myeloma database for patients with a diagnosis of MM who were treated in the Department of Hematology of Beijing Chaoyang Hospital from March 2005 to Aug 2013. Patients with EMP at diagnosis or during the course of MM were identified, and their demographic, clinical features , treatment, and outcome data were collected and analyzed. MM was defined according to the criteria of the International Myeloma Working Group1. We defined EMP as the presence of plasmacytomas in organs other

than bone. Patients with solitary plasmacytomas were excluded from participation in the study. The study was approved by the institutional review board. Patient and disease characteristics are shown in (Table1).

Table 1: Clinical and laboratory findings by patient group

Characteristics	Group 1（n=32）	Group 2（n=47）	p value
Age, years	53.5（41-72）	52（28-76）	NS
White cell count（$X10^9$/L）	3.2 (1.2-6.0)	4.6 (0.6-23)	NS
HGB（g/L）	90.5 (44-145)	105 (39-153)	NS
Platelets（$X10^9$/L）	172 (33-389)	185 (22-513)	NS
CRP（mg/L）	6.5 (0.5-60)	7.2 (0.16-97)	NS
ESR（mm/h）	102 (2-140)	43.5 (1-175)	NS
β_2MG（mg/L）	4.85(0.64-18.9)	3.25 (1.19-43.5)	0.028
Plasma cell（%）	52.5(3.5-92)	17.5 (1.5-93.5)	0.016
LDH(U/L)	192(63-321)	162 (52-762)	NS

c-reactive protein (CRP), serum lactate dehydrogenase (LDH), erythrocyte sedimentation rate(ESR), beta-2 microglobulin(β_2-MG)

3. Methods

The following analyses were routinely performed before and after chemotherapy: physical examination; measurement of serum creatinine, C-reactive protein (CRP), serum lactate dehydrogenase (LDH), beta-2 macroglobulin, and albumin levels; bone marrow aspirates and biopsy; urinary globulin electrophoresis and immunofixation. EMP was confirmed by magnetic resonance imaging (MRI), computed tomography (CT), or histopathological analysis.

Patients who developed EMP during the course of MM (group 1) received traditional chemotherapy, including melphalan, prednisone, and thalidomide (MPT), cyclophosphamide, prednisone, and thalidomide (CPT), and vindesine,epirubicin,dexamethasone, and thalidomide (VADT). When these patients developed EMP during the course of their disease, they were treated with a bortezomib-containing regimen or second-line chemotherapy regimens such as cisplatin, etoposide,cyclophosphamide, and prednisone (DECP). Patients who had EMP at the time of MM diagnosis (group 2) were treated with traditional chemotherapy regimens such as MPT or VAD or with bortezomib-containing regimens bortezomib cyclophosphamide, prednisone and thalidomide (VCPT) or bortezomib epirubicin, and dexamethasone（PAD). No patients received autologous stem cell transplantation.

Treatment responses were classified as complete remission (CR), very good partial remission（VGPR）, partial remission (PR), stable disease（SD）, and progressive disease (PD) according to the International Myeloma working group 2006 International unified clinical standards10. If the tumour was negative on MRI or CT, it was considered a complete response. Very good partial response was defined as a greater than 75% reduction in tumour size on MRI, partial response was defined as a 51-75% reduction, and minimal response was defined as a 25-50% reduction. We also assessed patients for adverse events, which we graded according to the National Cancer Institute Common Terminology Criteria (NCI-CTC) for Adverse Events version 3.0.

We used SPSS version 18.0 software for statistical analysis. Progression-free survival(PFS) and overall survival(OS) were analyzed using Kaplan–Meier survival curve.11. A p-value of less than or equivalent to 0.05 was considered statistically significant.

Ethics statement:

The study was conducted with the approval from the Ethics Committee of Beijing Chaoyang Hospital, Capital Medical University and all aspects of the study comply with the Declaration of Helsinki. Ethics Committee of Beijing Chaoyang Hospital specifically approved that not informed consent was required because data were going to be analysed anonymously，routine monitoring and patient records/information was anonymized .

4. Results

Among the 350 patients with MM, 79 (22.57%) patients were found to have EMP: 32 patients in group 1, and 47 patients in group 2. The median age was 56.2 years (range: 28–76 years), with 45 men and 34 women. Patients were followed up until Oct 31, 2014.(the median/mean follow-up duration was 42.8 months (range: 1–98months).

Of the 79 patients, 54% had stage III MM, 35% had stage II, and 11% had stage I, according to the International Staging System (ISS). MM was characterized as immunoglobulin G (IgG) in 41% of patients, light chain in 28%, IgA in 21%, non-secretory in 5%, and double clone in 5%.

Forty-four(55.7%) patients were diagnosed with EMP following complaints of bone pain (located in the waist/sacrum in 25 cases, the chest/back in 19 cases).For 21 patients, a mass was their major clinical manifestation of EMP. Twenty-eight percent of the patients presented with constitutional symptoms (disease-related anemia).Some patients also presented with fatigue and weight loss (8 cases); proteinuria (5 cases); decreased vision and eyelid drooping (3 cases). Six patients had onset of paralysis, and 15 had paralysis with disease progression. Pathological fractures occurred in 19 cases.(Table 2)

Table 2 Clinical symptoms of EMP

symptoms	Cases(n)
Bone pain	44
Mass	30
Paralysis	21
Pathological fracture	19
Fever	3
Weight loss	8
Proteinuria	15
Decreased vision and eyelid drooping	3
Hepatomegaly	4
Splenomegaly	12
Pleural effusion	23
Pericardial effusion	2
Plasma cell leukemia	2

The most frequent extramedullary location was muscle soft tissue (70%), most often in the chest wall and surrounding the ribs (42%) (Table II). Extra medullary plasmacytoma cells infiltrated the spinal canal in 50% of patients, a condition that often leads to paralysis12. Other sites involved included the eye, central nervous system, and heart13. Many patients (33%) had two involved sites (Table 3).

Table 3. Sites of EMP involvement

No. of cases	EMP site
Soft tissue	50
Skin	26
Spinal canal	36
Lymph nodes	13
Liver	4
Clavicle	8
Intra-abdominal	7
Retroperitoneal	3
Pleura/peritonea	23
Breast	2
CNS	2
Ovary	2
Heart	2
Eye	2
Kidney	1
Spinal canal	24

The treatment and outcomes of the patients with EMP varied according to whether the patients developed EMP after MM diagnoses, or were diagnosed with MM and EMP at the same time.

In group 1, 21 patients received the proteasome inhibitor bortezomib combined with DECP, 9 patients received traditional chemotherapy, and 2 patient did not receive treatment.In the 21 patients ten patients had a PR .3 patients remain stable, while 7 patients had PD and died. In this subgroup, the median survival duration was 33.6 months (range: 8–96 months) (Figure 1).

In group 2, 13 patients were treated with traditional chemotherapy: 7 had a PR, 3 had PD, and 3 died while on treatment. Thirty four patients were treated with combined bortezomib and chemotherapy: 18 patients reached CR and 13 patients had a PR. In this subgroup, the median survival duration was 21 months (range: 1–52 months) (Figure 1). Fourteen patients died; the causes of death were multiple organ failure (3 cases), respiratory failure(3 cases), cerebral hemorrhage (5 cases), tamponade(2 cases), and uremia (1 case).

5. Discussion

Of the 350 consecutive MM patients who we evaluated, 79 (22.6%) MM patients have EMP, this proportion was little higher than the 20% reported.9,14-16 Research indicates that patients with MM and EMP have different characteristics and outcomes than patients with MM alone. It is important to recognize that although the cortical bone and medullary compartment are anatomically linked, they are functionally distinct, and in most patients with EMPs, soft-tissue tumors arise as direct extensions from skeletal tumors when they disrupt the cortical bone. The remaining tumors result from hematogenous metastatic spread.

Our patients were more than 10 years younger, on average, than those in a previous study 17. In our study,65.3% of the EMPs were found at diagnosis. In 2 recent studies, 68% and 85% of EMPs observed at diagnosis were soft-tissue masses adjacent to bone lesions, whereas the remaining 32% and 15% of plasmacytomas, respectively, resulted from

hematogenous spread18. In most of our patients, the first symptom of EMP was bone pain, but unlike MM, EMP often presents as a mass, which indicates that extramedullary invasion is the first symptom.

In our study, patients with EMP most often had IgG myeloma (41%), followed by the light chain type (28%). A high frequency of extraosseous involvement has been reported in IgD myeloma19. Any organ can be involved, even the CNS. We reported 2 cases (3%) of CNS involvement; a previous study showed a 1% rate of CNS involvement 20,21. Once CNS involvement occurs, the median survival time is only 3 months20. Because EMP can occur anywhere, the clinical manifestations are multiple and the risk of misdiagnosis is high. Therefore, it is important to perform an imaging examination when EMP is suspected.

Recent research has indicated that the bone marrow microenvironment plays a key role in the pathogenesis of MM by triggering signaling cascades that mediate myeloma cell proliferation, migration, and survival, contributing to myeloma growth and the homing of malignant plasma cells(PCs)within the bone marrow. Decreased expression of adhesion molecules and homing failure are the 2 most important factors20.

The treatment of these patients was unsatisfactory. For isolated plasmacytoma ，the main treatment is surgery or radiotherapy.In our study all patients were not isolated and not suitable for radiotherapy. At diagnosis, extramedullary disease can be sensitive to conventional agents, radiotherapy, and high-dose therapy. Of the patients with EMP at diagnosis, 81% achieved at least a partial response to initial therapy. Previous studies have shown that thalidomide treatment increases the risk of EMP in patients with MM8. But in our series, there was no correlation between prior treatment with thalidomide and EMP. We did, however, find that patients previously treated with bortezomib had a lower EMP risk. Since our study was retrospective and not prospective, the results regarding prior therapies in EMP have to be judged cautiously, and definite conclusions cannot be drawn. A previous large study in patients with MM and extramedullary disease did not find any association between prior treatment with bortezomib, thalidomide, or lenalidomide and higher risk of extramedullary spread 9. For lenalidomide was not approved by China Food and Drug Administration (CFDA) until July 2013,so these patients have none used this drug.

MM patients with EMP have a poor prognosis8 and shorter progression-free and overall survival than patients without EMP (Figure 1). The Royal Marsden group reported that the presence of EMPs at diagnosis was associated with poorer prognosis in patients treated with conventional chemotherapy16. In our analysis, 47 patients presented with EMP at diagnosis. The median OS duration was 21 months, significantly lower than statistics MM 3-5 years with the comparison to the patients who were not combinated with EMP.For the group 1,if defined the time which developed an EMP to death as overall survival 1(OS1).The OS1 was 14 months shorter than group1 and group2.

Systemic chemotherapy is required to control the EMP. It has been suggested that new antimyeloma agents, particularly thalidomide and bortezomib, could be effective for the treatment of extramedullary myeloma22,23. However, it seems that there is no role for thalidomide therapy20. In our study, 54 patients were treated with a bortezomib-chemotherapy combined regimen, and 18 of those patients had a CR. In contrast, of the 17 patients treated with traditional therapy, none had a CR. In the aggressive terminal phase of MM, myeloma cells become independent of the bone marrow stroma. The myeloma then becomes essentially resistant to chemotherapy and survival times are poor, even with high-dose chemotherapy.

In conclusion, myeloma with EMP is not a rare disease. A better understanding of the pathophysiology and molecular components of MM and EMP is urgently needed for the development of new, more effective treatments.

Disclosure

The authors declare that there were no conflicts of interest in this work.

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Yuping Zhong performed the study and wrote this paper. Jiajia Zhang collected and analysed the data.

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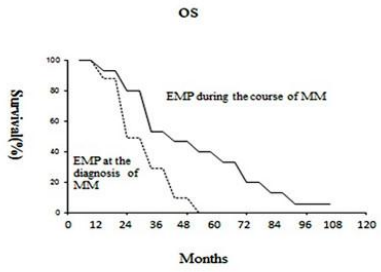
Figure 1 Survival of two groups of patients with EMP that developed at the time or after the diagnosis of MM

Figure 1. Survival of two groups of patients with EMP that developed at the time of or after the diagnosis of MM.



Showed that the presence of EMPs at diagnosis was associated with poorer prognosis in patients treated with conventional chemotherapy.

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