Soft-tissue extramedullary multiple myeloma prognosis is significantly worse in comparison to bone-related extramedullary relapse

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ABSTRACT

Even in the era of new drugs, multiple myeloma patients with extramedullary relapse have a poor prognosis. Our goal was to analyze the frequency and outcome of extramedullary relapse occurring in relapsed multiple myeloma patients. In total, we analyzed the prognosis of 226 relapsed multiple myeloma patients treated between 2005 and 2008 and evaluated them for presence of extramedullary relapse. We found evidence of extramedullary relapse in 24% (55 of 226) of relapsed multiple myeloma patients. In 14% (32 of 226) of patients, the lesions were not adjacent to the bone, while extramedullary relapse adjacent to the bone was documented in 10% (23 of 226) of cases. Patients without extramedullary relapse had significantly longer overall survival than patients with extramedullary relapse (109 *vs.* 38 months; $P<0.001$). Moreover, patients with soft tissue-related extramedullary relapse had significantly poorer overall survival compared to bone-related extramedullary relapse patients (30 *vs.* 45 months; $P=0.022$). Also, overall survival from diagnosis was as low as five months for soft tissue-related extramedullary relapse patients when compared to 12 months overall survival for bone-related extramedullary relapse. This is the first study that shows a significant difference in prognosis for different types of extramedullary relapse. If the extramedullary myeloma infiltration was not bone-related, overall survival after relapse was extremely short (5 months).

Introduction

Multiple myeloma (MM) is characterized by malignant proliferation of clonal plasma cells that usually produce a unique monoclonal immunoglobulin. MM comprises approximately 1% of all cancers and is the second most common hematologic malignancy.[1] Unfortunately, the etiology of MM is still unknown.[2] Current treatment strategies combine novel agents, such as thalidomide, bortezomib, lenalidomide, with conventional chemotherapy, corticosteroids and autologous stem cell transplantation and significantly prolong long-term patient outcome. More than 30% of patients undergoing intensive treatment live for more than ten years, and there is a clear but limited possibility for some patients with low-risk disease to be cured.[3] However, relapse is still a frequent event; whenever it occurs, there is no chance for a cure with current treatment options. Even in relapsed disease, remissions can be obtained in the majority of patients[4,5] although these tend to be shorter than first treatment responses.[6,7] Extramedullary myeloma is not frequent but is always associated with a significantly shorter overall survival, even in the era of novel agents.[3,8-12]

Extramedullary myeloma (EM) is a type of MM defined by the presence of extraskeletal (i.e. soft tissue or visceral) clonal plasma cells infiltrates.[13] EM can be present either at the time of initial diagnosis (primary EM) or at the time of relapse (secondary EM).[3]

Clinically, three types of extramedullary lesions can be described: a) tumor mass adjacent to bone and extending into soft tissues; b) soft tissue or visceral tumor that is not connected to the bone; or c) diffuse infiltration of organs by plasma cells without any obvious focal lesion. However, the majority of studies do not discriminate between these three types of EM lesions.

There are very few large studies focusing on incidence of EM. Primary EM is found in approximately 4-16% of MM patients at the time of diagnosis. Secondary EM is found in 6-20% during further MM disease course.[14] Unfortunately, the prognosis of EM patients is generally poor, and there is no effective treatment for EM.[15]

The primary objective of this study was to analyze the frequency and outcome of secondary EM occurring in relapsed MM patients. In addition, we identified the clinical difference and outcome of bone-related and bone-unrelated subtypes of EM.

Methods

All consecutive relapsed MM patients (in total 226 patients) treated in our department at the University Hospital Brno, Czech Republic, between 2005 and 2008 were included in this analysis and prospectively evaluated for the presence of EM. They were included in this study only after signing the informed consent form approved by the Ethical Committee of the hospital.

The median age of patients was 60.8 years (range 27.9-83.5), and the median follow up was 3.7 years (range 0.1-22) after diagnosis. Other base-line patients' characteristics are shown in Table 1. Out of 226 MM patients, we excluded 6.2% (15 of 226) of patients with pri-

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mary EM, i.e. evidence of extramedullary disease at the time of MM diagnosis.

EM was diagnosed using imaging methods, such as ultrasound, computed tomography (CT) or magnetic resonance (MR). Biopsies were carried out if the lesion was accessible to confirm the presence of clonal plasma cells on cytological or histological examination. EM was defined as the presence of a pathological soft tissue mass by imaging in patients with other findings compatible with MM progression/relapse or a finding of clonal plasma cells in biopsy or aspirate from the extramedullary lesion. Patients with clinical suspicion of extramedullary progression underwent further examinations. All patients with new neurological symptoms had MRI of spine or brain if there were no contraindications. All patients with leptomeningeal infiltration had lumbar punction with flow-cytometric evaluation of cerebrospinal fluid. If there were some contraindications, CT was performed. Ultrasound was performed in patients with hepatic lesion and also if soft tissue infiltration was suspected.

Patients with EM were divided into two groups: 1) soft tissue-related EM (EM-S), i.e. the presence of soft tissue or visceral masses not linked to skeletal involvement by MM, or diffuse organ infiltration by malignant plasma cells; 2) bone-related EM (EM-B), i.e. a plasma cell mass adjacent to a bone lesion.

Overall survival (OS), time to EM, and previous treatments were analyzed for both groups of patients. The treatment was rather heterogeneous but all patients had received either thalidomide or bortezomib prior to relapse. EM therapy consisted of a novel agent that had not been used previously, in combination with corticosteroids and chemotherapy. Patients with a good performance status and available stem cell autograft received high-dose chemotherapy with melphalan followed by stem cell rescue. Regimens used for EM treatment included thalidomide in 33% of patients, bortezomib in 38% and lenalidomide in 5%. Forty-two percent of patients were treated with high-dose melphalan and stem cell transplantation. Chromosomal abnormalities were evaluated using FISH as reported previously.[16-18]

Statistical analysis

Kaplan-Meier estimates were used for survival analysis. Differences between survival times in patient subgroups were tested using the log rank test. Differences in categorical variables were analyzed using the M-L χ^2 test. The level of statistical significance was 5% for all tests.

Results

We found evidence of EM in 24% (55 of 226) of evaluable relapsed MM patients. In 14% (32 of 226) of these patients, the lesions were not adjacent to bone and thus were classified as EM-S, while EM-B was documented in 10% (23 of 226) of cases. In the EM-S group, the most common site of EM was skin and subcutaneous tissue (69%), while extramedullary masses extending from vertebrae (78%) were most common in the EM-B group. Histological evaluation was performed in 66% of proven EM cases. In other cases, MRI (22%), CT (4%) and ultrasound (2%) were used for proven EM cases (Table 2). EM occurred early in the course of the disease: for 53% of patients (29 of 55 patients) at first relapse, 33% (18 of 55) at second relapse, 14% (8 of 55) at third and higher relapse. In both groups, more than half of patients were diagnosed with EM during the first relapse (Table 3). Time from diagnosis to EM relapse was similar for both EM-S and EM-B groups and the difference was not statistically significant (21 *vs.* 23 months).

Conventional chemotherapy was used in 20% (11 of 55) of patients prior to EM relapse. Thalidomide-containing regimens, bortezomib-containing regimens and high-dose chemotherapy with autologous stem cell transplantation had been given to 38% (21 of 55), 29% (16 of 55) and 53% (29 of 55) of patients, respectively. Differences in the treatment regimens of EM-B and EM-S groups prior to relapse were not statistically significant (Table 4).

Median OS for all the 226 MM patients followed was 89 months with median follow up of 44.4 months (range 6.5-264). There was no difference in incidence of EM in gender (P=0.54) or median age at the time of EM diagnosis (P=0.132).

Overall survival was significantly longer for patients without EM than for patients with EM (109 *vs.* 38 months; P<0.001) (Figure 1A). However, there were no differences

Table 1. Patients' characteristics.

Characteristics	N.
Gender M/F	115/111
Median age in years (range)	60.8 (27.9-83.5)
Durie-Salmon stage I/II/III	35/41/148
Durie-Salmon stage A/B	187/37
Isotope: IgG/IgA/LC/other	135/50/25/16
Light chain: kappa/lambda	142/74
ISS stage I/II/III	57/65/37
Median follow-up in years after diagnosis (range)	3.7 (0.1-22)
EM-S	32
EM-B	23

ISS: International Staging System. In total, 226 MM patients were analyzed. EM-S: extramedullary relapse - soft tissue; EM-B: extramedullary relapse - bone related.

Table 2. Organ involvement of 55 patients with extramedullary relapse of multiple myeloma

Involved organ	N. (%)	Biopsy (%)
Bone related - in total (EM-B)	23 (41.8)	8 (14.6)
Bone related - spine	18 (32.7)	4 (7.3)
Bone related - other	5 (9.1)	4 (7,3)
Soft-tissue related - in total (EM-S)	32 (58.2)	28 (51%)
Skin	22 (40)	22 (40)
Central nervous system	2 (3.6)	2 (3.6)
Retroperitoneal tumor mass	4 (7.3)	2 (3.6)
Lungs	2 (3.6)	0
Lymph nodes	1 (1.8)	1 (1.8)
Liver	1 (1.8)	1 (1.8)

Table 3. Occurrence of extramedullary lesions in relapse of MM.

	EM-B, N. (%)	EM-S, N. (%)
1st relapse	12 (52.2)	17 (53.1)
2nd relapse	7 (30.4)	11 (34.4)
3rd relapse	2 (8.7)	3 (9.4)
4th relapse	1 (4.3)	1 (3.1)
6th relapse	1 (4.3)	0 (0.0)

in overall response rate (ORR) or complete response rate (CR) in first-line treatment between these two groups (*P*=0.201). Also, TTP after first-line treatment was similar in patients with and without EM (20 months vs. 16 months; *P*=0.112). Interestingly, we did not find any difference between TTP after first-line treatment between the EM-B and EM-S groups of patients (14 months *vs.* 18 months; *P*=0.128).

Overall response rate after EM relapse was as low as 24% (13 of 55) in EM patients, with 5% (3 of 55) and 19% (10 of 55) of patients achieving complete and partial responses, respectively. Time to next progression (TTP) was only 5.4 months in EM patients.

When we analyzed the two groups of EM patients, we found that the EM-S group of patients had significantly poorer survival compared to EM-B patients (30 *vs.* 45 months; *P*=0.022) (Figure 1B). Analysis of OS from diagnosis of EM confirmed the poorest outcome for patients with EM-S when compared to EM-B (median OS 5 *vs.* 12 months; *P*=0.006) (Figure 2).

Results of cytogenetic analysis using FISH at the time of diagnosis were available for 22% (38 of 171) of patients without EM and 24% (13 of 55) of EM patients. The following chromosomal abnormalities with presumed impact on the prognosis of MM[16,17] were studied: RB1 deletion, p53 deletion, IgH gene disruption, translocation t(4;14), amplification 1q21 and hyperploidy. No differences were shown in the incidence of any of these chromosomal abnormalities between EM patients and those without EM (Table 5).

Discussion

Even in the era of new drugs, extramedullary relapse remains incurable. EM has been mostly studied in MM patients treated with high-dose chemotherapy, and most published studies evaluated patients at first relapse.[9,19-21] The incidence of EM has been estimated to be 10-15% of all MM relapses.[8,9,13] Recently, Usmani *et al.* analyzed 1965 MM patients for presence of EM at the time of MM diagnosis and at the time of relapse. The presence of extramedullary disease at the time of diagnosis was reported between 2.41% and 4.5% depending on the type of therapy. At the time of relapse/disease progression, extramedullary involvement was noted in 3.43-7.24% of patients.[3] In our cohort of 226 relapsed MM patients, the incidence of EM, after excluding all patients with known extramedullary disease at the time of diagnosis, was 24%, including 14% of EM-S and 10% of EM-B, respectively. However, the absence of an exact EM definition and consequently different format of EM calculation and reports make correct comparison difficult, even between trials.

In our study, we systematically analyzed all consecutive

Table 4. Treatment of patients before diagnosis of extramedullary relapse.

Treatment	EM-B, n. (%)	EM-S, n. (%)
Conventional regimens	6 (26.1)	5 (15.6)
Thalidomide	9 (39.1)	12 (37.5)
Bortezomib	5 (21.7)	11 (34.4)
Autologous transplantation	13 (56.5)	16 (50.0)
Interferon alfa	11 (47.8)	11 (34.4)

Table 5. Cytogenetic aberrations of MM patients. We found cytogenetic aberrations in 51 patients at the time of diagnosis, in 38 patients without and 13 patients with extramedullary relapse. There was no statistical difference in incidence of aberrations between both groups.

	EM relapse n. (%)	No EM relapse n. (%)	*P* level
Deletion RB1 positive	13 (54)	37(62)	0.744
Deletion p53 positive	6 (33)	25 (8)	*
IgH gene disruption positive	10 (80)	18 (61)	0.417
Translocation t(4;14) positive	12 (33)	26 (31)	1.00
Gain 1q21 positive	9 (56)	28 (50)	1.00
Hyperdiploidy positive	4 (0)	14 (36)	*

*N: number of patients evaluated; %: percent of patients with positive aberration out of n patients; * analysis not performed due to low number of patients.*

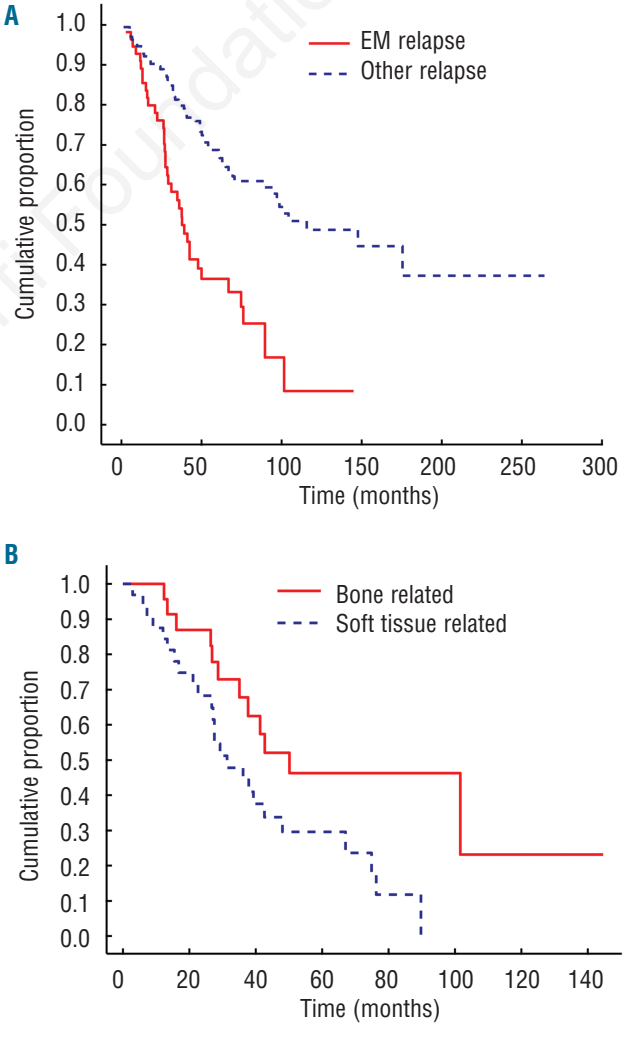

Figure 1. Overall survival and survival from diagnosis of EM patients. (A) Overall survival from diagnosis in patients with extramedullary relapse (EM) is significantly shorter than in other MM patients (38 *vs.* 109 months *P*>0.001). (B) Comparison of survival from diagnosis in patients with bone related extramedullary relapse (EM-B) is significantly longer than in patients with soft-tissue related extramedullary relapse (EM-S) (30 *vs.* 45 months; *P*=0.022)

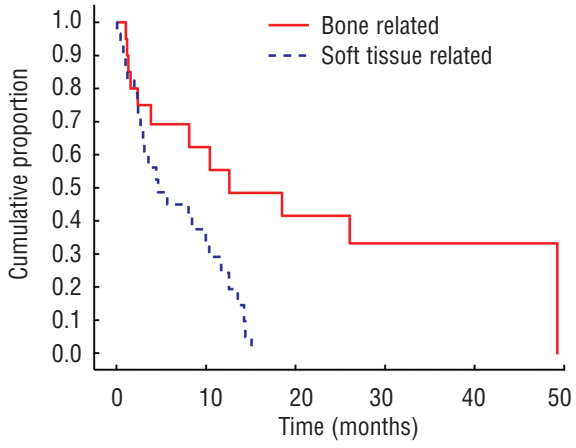

Figure 2. Overall survival from diagnosis of patients with bone related extramedullary relapse (EM-B) is significantly longer than in patients with soft-tissue related extramedullary relapse (EM-S) (4 *vs.* 12 months; *P*=0.006).

patients who relapsed during a 3-year period, from 2005 to 2008; up to 53% of EM occurred in the first relapse. We were not able to detect any association between EM relapse and any novel agent (thalidomide or bortezomib). In this single center experience, EM-B was observed only in 2% (4 of 113) of patients who underwent initial therapy with classical treatment protocol without any novel agents in the period 1996-2002 (4 x VAD and melphalan 200 mg/m^2).[22]

The most important finding in our analysis is the significant difference in prognosis for the two different types of EM. In accordance with the results of most research groups, we noted survival of approximately 12 months in our EM patients if the extramedullary mass was adjacent to the bone. However, if the extramedullary myeloma infiltration was not bone-related, the overall survival was extremely short and not longer than four months.

Based on these results, it is possible to divide patients with EM relapse into two different prognostic groups: 1) 'bone-related' extramedullary myeloma (EM-B), i.e. myeloma mass is adjacent to a distinct bone. The patients with this type of EM have an OS that is less than 50% shorter than patients who relapse without the EM component; 2) 'bone-unrelated' extramedullary myeloma (EM-S), i.e. myeloma mass of soft tissue with no relation to the bone. Such patients have the worst prognosis with a limited OS of less than 4-6 months. This would suggest that the biological behavior of these two types of EM is probably different.

Clear identification of one type of EM from another is now easily available with widespread use of PET/CT and/or whole body MRI and should be standardized in every future published cohort of EM patients. Our analysis covers only the relapsed setting, and the prognostic significance of the subtype of EM remains to be validated in primary EM. Thus, we believe that all studies analyzing EM should include details about primary or secondary EM as well as division of patients into EM-S and EM-B groups.

We completely excluded patients with primary EM from our analysis. We strongly believe that it is important to do so as we found that OS and TTP are similar after first-line treatment in all MM patients. However, survival rapidly decreases if EM develops during the course of the disease. Similarly, the presence of EM at the time of diagnosis was a very strong negative prognostic factor in the Arkansas analysis; it was the only parameter that was significantly important in all groups of patients. Also, patients with primary EM had the worse prognosis.[3] According to these data and our results, it is clear that the prognosis of MM patients is similar until the development of EM. But after this event, survival is very poor for patients with EM regardless of whether it is primary or secondary EM.

Our cohort of relapsed EM patients is one of the largest ever published. While no patient with skin and subcutaneous plasmocellular masses was seen in our center prior to 2005, as many as 22 cases were diagnosed between 2005 and 2008. It is likely that the recent changes in treatment strategies are associated with the increased incidence of EM, although the trend is unlikely to be associated with any particular drug. Our results suggest that the incidence of soft tissue EM is increasing in the era of novel drugs. These data need to be confirmed in prospective studies and comparative studies with historical controls. Many analyses, including ours, show that survival of MM patients has improved significantly after the implementation of novel therapeutic regimens.[2,11,12,22,23] However, patients with EM generally do not benefit from these agents and their survival remains extremely poor. Thus, EM remains one of the major ongoing issues in the care of MM patients.

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Authorship and Disclosures

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