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REVIEW

Incidence of extramedullary disease in patients with multiple myeloma in the era of novel therapy, and the activity of pomalidomide on extramedullary myeloma

K Detweiler Short[1], SV Rajkumar[1], D Larson[2], F Buadi[1], S Hayman[1], A Dispenzieri[1], M Gertz[1], S Kumar[1], J Mikhael[3], V Roy[4], RA Kyle[1], MQ Lacy[1]

[1]*Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA;* [2]*Department of Biostatistics, Mayo Clinic, Rochester, MN, USA;* [3]*Division of Hematology/Oncology, Mayo Clinic in Arizona, Scottsdale, AZ, USA and* [4]*Division of Hematology/Oncology, Mayo Clinic in Florida, Jacksonville, FL, USA*

We studied 174 consecutive patients with relapsed refractory multiple myeloma (MM) enrolled on a phase II clinical trial of pomalidomide plus low-dose dexamethasone at Mayo Clinic. Extramedullary disease (EMD) was present at the time of trial entry in 7.5% (13 of 174 patients). The rate of EMD in the first 3 years following diagnosis of MM was 3%. The response of EMD to pomalidomide plus low-dose dexamethasone included two complete and two partial responses among the 13 patients (response rate, 31%). Overall survival measured from trial entry was significantly shorter for patients with treatment-emergent EMD compared with those who did not have EMD, (median 16 months versus not reached, $P=0.002$).
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Multiple myeloma (MM) is a malignant plasma cell proliferative disorder typically contained within the bone marrow (medullary disease).[1] Infrequently, extramedullary disease (EMD) occurs with the presence of malignant plasma cells outside of the bone marrow within soft tissue, lymph nodes, muscle, skin and other organs (extramedullary myeloma).[2,3] True EMD is uncommon at the time of initial presentation of MM. In a series of 1027 patients with newly diagnosed MM, only four patients (0.4%) had EMD at the time of first diagnosis.[4] EMD is more often seen with relapsed refractory disease, and may be associated with decreased overall survival.[2]

There is some concern about a rise in the incidence EMD in the era of novel therapy, and the response of EMD to novel agents.[3,5,6] However, it is difficult to ascertain the true incidence of EMD during the course of MM because many studies include disease extending from bone as 'extramedullary.' Further, as screening techniques improve with increasing use of computed tomography, positron emission tomography, and magnetic resonance imaging studies in MM, it has become harder to determine if there is a real change in the incidence of EMD.

The purpose of this study was to determine the incidence of treatment-emergent EMD in MM among a cohort of patients who have been previously exposed to one or more novel agents (thalidomide, lenalidomide, or bortezomib), and to evaluate the activity of pomalidomide in patients with EMD.

Correspondence: Dr MQ Lacy, Department of Internal Medicine, Division of Hematology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA.
E-mail: lacy.martha@mayo.edu
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Methods

We studied the detailed medical records of 174 consecutive patients with relapsed refractory MM that were enrolled on a phase II clinical trial of pomalidomide plus low-dose dexamethasone at Mayo Clinic from 1 November 2007 to 12 May 2010. The study cohort was specifically selected since all patients had previously been exposed to novel agents, and all were followed systematically and received uniform therapy with pomalidomide plus low-dose dexamethasone. We adopted a strict definition of EMD, which required that to be considered extramedullary, plasmacytomas must not have risen from any bone. Thus, masses arising from the bone with a soft tissue component were not considered extramedullary.

Results and discussion

Of 174 patients studied, 16 patients (9.2%) had EMD. In 3 of the 16 patients, EMD was present at time of first diagnosis of MM. The rate of treatment-emergent EMD during the course of MM therapy was 7.5% (13 of 174 patients) in patients entering the clinical trial (Table 1). The median number of lines of previous therapy in these patients was 6, (range 1–12). The EMD sites involved included the temporal area (not arising from the skull) soft tissue (3), muscle (3 (1 pt with 10 different areas of involvement, 1 pt with 5 areas involved)), chest wall not attached to bone (3), abdominal/pelvic masses (3), kidney (2), scrotum (2), sinus (1), paraspinal (1), hilar/pleural based (1), paraesophageal (1), subcutaneous tissue (1), pancreas (1), spleen (1), mediastinum (1), pleural fluid (1), liver (1). The median number of extramedullary sites per patient was 1, although there was one patient with 11 sites and one with 20 sites (range 1–20 sites per patient).

On the basis of our inclusion criteria, all 13 patients with treatment-emergent EMD had previously received novel agents. In 100% of patients, exposure to immunomodulatory agents (thalidomide or lenalidomide) occurred before the diagnosis of EMD; 78% (10 patients) had previous exposure to bortezomib. Treatment-emergent EMD occurred a median of 48 months following diagnosis (range, 16–183 months); the rate of treatment-emergent EMD in the first 3 years following diagnosis of MM was 3%. As all patients had previous exposure to immunomodulatory agents in this cohort, we were able to calculate the median length of time from initiation of immunomodulatory agents to onset of EMD as 24 months (range 7–119 months).

Per protocol, all patients received pomalidomide (2–4 mg per day) and low-dose dexamethasone (40 mg once a week). Of the

Table 1 Characteristics of patients with extramedullary myeloma

Patient	*Time from diagnosis to EMD (months)*	*No. of EMD sites*	*Sites of EMD*	*No. of previous regimens*	*Response of M protein*	*Response of EMD*	*Mode of diagnosis*
1	21	1	Soft tissue	5	Unevaluable	Progression after 1 cycle	Physical examination and PET
2	59	Innumerable	Soft tissue, liver, kidney, spleen, muscle, pleura, lung	8	MR	Mixed response after 3 cycles	Physical examination and PET
3	180	Multiple	Soft tissue	7	PR	PR after 2 cycles	Physical examination and PET
4	21	1	Iliac fossa	3	Stable Disease	Unevaluable	Physical examination, CT abdomen and PET
5	70	1	Soft tissue	10	Stable Disease	Stable disease (6 cycles)	PET
6	19	1	Cavernous sinus	3	Progression	Progression after 1 cycle	MRI
7	86	1	Soft tissue	10	VGPR	Not evaluated	Imaging
8	68	Multiple	Liver	10	Progression	Not evaluated	PET
9	120	1	Pleura	6	Stable Disease	Not evaluated	Ultrasound
10	18	2	Psoas muscle, scrotum	7	Progression	Not evaluated	Physical examination, CT abdomen and PET
11	42	3	Perinephric, soft tissue, muscle	6	VGPR	PR after 2 cycles	Imaging
12	40	7	Soft tissue, mesentery, retroperitoneum, muscle	6	Unevaluable	Progression after 1 cycle	Physical examination and PET
13	32	2	Perinephric, soft tissue	5	Unevaluable	CR after 3 cycles	CT abdomen

Abbreviations: CT, computed tomography; CR, complete response; EMD, extramedullary disease; MRI, magnetic resonance imaging; PR, partial response; PET, positron emission tomography; VGPR, very good partial response.

13 patients with EMD, two achieved complete response (with complete disappearance of EMD), two had partial response ($\geqslant$50% reduction in EMD) and two stable disease. In three patients, the best response was progressive disease; four patients did not have their EMD re-evaluated. Of the four patients who had a 50% or greater reduction in size of the EMD (response rate, 31%), one patient had received concomitant radiation. Overall survival measured from trial entry was significantly shorter, for the 13 patients who had EMD, compared with those who did not have EMD, (median 16 months versus not reached, $P=0.002$ (log-rank), Figure 1).

Our study assessed the incidence of strictly defined EMD that develops during the course of MM in patients who did not have EMD when MM was first diagnosed (treatment-emergent EMD). We specifically excluded extramedullary extension of bony disease from consideration because our interest was in the incidence and response of EMD in which clonal plasma cells were able to proliferate outside the confines of the bone marrow microenvironment. We felt that disease extending from bone merely represented greater tumor bulk of typical MM, but not necessarily a different biologic entity. Our study has three main conclusions. First, we establish that 7.5% of patients with relapsed refractory myeloma in the era of novel agents developed treatment-emergent EMD during the course of their disease. In total, 3% developed EMD within 3 years of diagnosis. This is an important benchmark that allows us to compare rates across studies and time-periods. Our estimates are lower than rates previously reported as we excluded soft tissue extensions of bony plasmacytomas from consideration. We prefer the term 'treatment-emergent EMD' rather than treatment-related EMD as it is not clear if the treatment played any role in the occurrence of EMD.

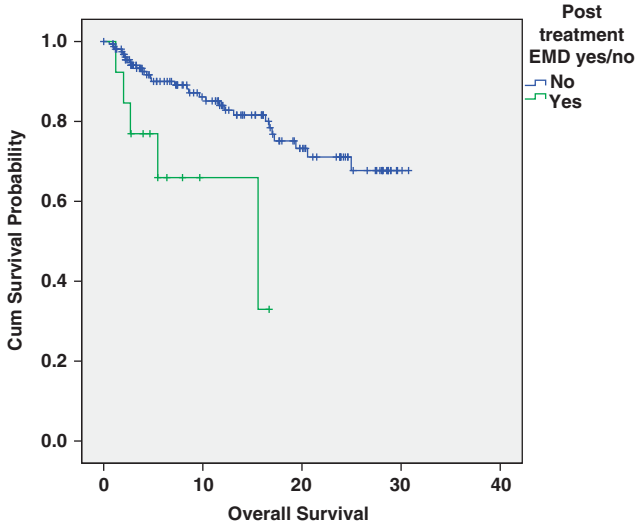

Figure 1 Overall survival. Kaplan–Meier plots showing inferior survival from trial entry in patients with extramedullary plasmacytoma compared with patients without extramedullary disease. EMD, extramedullary disease.

Second, our study shows that EMD does respond to the new immunomodulatory drug pomalidomide with a response rate of $\sim$30% including the extramedullary component. Third, we show that the overall survival of patients who develop EMD is significantly shorter than patients without EMD, suggesting that either EMD represents clonally advanced disease or greater tumor bulk, or both.

There are some caveats. The incidence rates of EMD will be affected by the type and frequency of imaging studies used, including sensitive positron emission tomography/computed tomography and magnetic resonance imaging. In our study, 54% of ($n = 6$) patients were diagnosed based only on imaging studies (there was no evidence of EMD on physical exam). Another factor is the improved overall survival of patients with novel agents. Thus, part of any increased incidence in EMD may be related to the fact that MM patients have a greater number of years at risk now than before. However, one way to overcome this is to determine the incidence over a defined time-period. In our cohort, the rate of EMD in the first 3 years following diagnosis was 3%. An important consideration that requires further studies to answer is whether novel agents increase the risk for strictly defined, EMD in a small subset of patients. One hypothesis is that the high activity of new treatments may result in the near total eradication of sensitive clonal cells, but as a consequence facilitate the emergence of a resistant, inherently aggressive clone. Novel agents have revolutionized the treatment of MM, but we need more follow up to determine the long-term side effects of these agents. Future studies should compare the molecular cytogenetic features between the bone marrow and EMD tissue. We need to identify specific cytogenetic features associated with EMD and its outcome, and also determine whether such features are associated with poor outcome in patients without overt EMD.

Conflict of interest

MG has received honoraria from Celgene, Millennium, Genzyme and Amgen. SK has received research support from Celgene, Novartis, Millennium, Bayer and Genzyme. MQL and AD have received research funding/grants from Celgene. The remaining authors declare no conflict of interest.

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