

Extramedullary Myeloma

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Editorial

Extramedullary myeloma (EMM) is the presence of clonal plasma cells (PCs) outside the bone marrow in a patient with multiple myeloma (MM). EMM can be present at the time of initial diagnosis (primary EMM) or at the time of relapse (secondary EMM) [1]. EMM has an incidence of 7% to 20% at presentation and 6% to 20% during disease progression [2]. Using sensitive imaging techniques including MRI and PET/CT, EMM may be found in up to 30% of MM patients across the overall disease course [3].

Blade et al. [4] proposed two distinct mechanisms of EMM: direct extension of bone plasmacytomas with cortical destruction and hematogenous dissemination of myeloma cells to an anatomical site distant from the bone marrow. Extramedullary spread can be triggered by an invasive procedure (surgery or catheter insertion) or by a bone fracture [3].

Weinstock & Ghobrial [5] as well as Touzeau et al. [3] have recommended restricting the definition of EMM to purely extramedullary disease and excluding bone-related plasmacytomas arising from the neighboring bone marrow due to the presence of significant differences in the biological and prognostic characteristics of these two entities. The molecular mechanisms underlying hematogenous spread of PCs outside the bone marrow are only partially known and involve hypoxia and an altered expression of adhesion molecules [3]. PCs in EMM are characterized by under expression of CD56 [2] adhesion molecule and overexpression of CD44, which is involved in cell proliferation and migration. The increased expression of CXCR4 and its ligand CXCL12 [6] have also been implied to contribute to the dissemination of PCs [3].

Plasma cell leukemia patients are prone to develop extramedullary disease at sites of catheter placement or surgery which may be linked with longer persistence of plasma cells in the blood [7]. Age and number of prior therapies were associated with a higher risk of extramedullary relapse [8]. A previous study

indicates that extramedullary progression seems to increase with thalidomide therapy, even in patients with good serological and marrow response [9]. Novel agents including lenalidomide and bortezomib seem not to increase the risk of EM disease [10].

A higher incidence of extramedullary relapse was reported in patients underwent allogeneic stem cell transplantation [3]. The use of lenalidomide prior to the allogeneic transplant was found to be a protective factor [3]. EMM mostly involve liver, skin, CNS, pleural effusion, kidneys, lymph nodes, and pancreas [3]. Skin was the most frequent location at diagnosis while liver involvement and pleural effusion were the most striking feature at progression [2,6]. At the time of extramedullary disease, 28% of patients with EM disease had experienced weight loss and disease related fever which are rare in myeloma patients without extramedullary disease [11].

Usmani et al. [12] have suggested that patients with EM disease may share characteristic laboratory features including lower hemoglobin levels, higher LDH levels and increased rates of thrombocytopenia relative to marrow-localized MM patients. 93% of patients with extramedullary disease demonstrated elevated serum LDH and less median paraprotein level in the blood at extramedullary relapse than that at diagnosis [11]. In addition, patients with relapsed EMM may present with light-chain escape (i.e, a shift from secretion of intact immunoglobulin to free light-chain only secretion) [13]. Extramedullary disease PCs show a high frequency of p53 and ras mutation and up regulation of FAK [3].

PET-CT is probably the technique of choice to detect extramedullary disease and is an important tool during follow-up [14]. Confirmation of the diagnosis of EMM through a biopsy is highly recommended as it may provide the biological rationale for targeted therapy in some cases (eg, BRAF mutated plasmacytoma) [3]. Extramedullary disease is associated with adverse prognostic factors (i.e., high LDH level, 17p deletion and high-risk gene expression MAF and PR profile). Weinstock et al. [6] suggested that neither hemoglobin level nor LDH level is a

reliable predictor of MM patients with EMM or going to develop EMM during the course of their disease.

EMM has poor outcome whether detected at presentation or during follow-up. The total number of EM sites did not determine the outcome as patients with both solitary and multifocal EMM had similar outcome. However, the anatomic location of EMM at some sites did influence outcome [15]. EMM involving the liver, lung, and muscles was associated with shorter survival compared with involvement in other anatomic sites [15]. Patients with soft tissue extramedullary relapse had significantly poorer overall survival compared to bone related extramedullary relapse [1]. The overall survival from diagnosis was low as five months for soft tissue related EM relapse patients when compared to 12 months overall survival for bone related EM relapse [1].

No prospective therapeutic studies have been specifically dedicated to EM patients. Experts consider de novo EMM as high-risk disease and recommend aggressive treatment of patients, if possible. For de novo EM patients eligible for stem cell transplantation, it is proposed to give a triplet induction therapy followed by high-dose melphalan /ASCT, a triplet consolidation therapy and a maintenance treatment, consisting of at least lenalidomide [3]. For high-risk patients, some propose the routine use of tandem ASCT.

For elderly MM patients not eligible for ASCT, bortezomib melphalan-prednisone (VMP) or continuous Len-Dex are currently two of the most effective up-front therapy. Their impact on the outcome of EMM patients is currently unknown [3]. The molecular characterization of PCs may help to guide therapy. Andrulis et al. [16] reported a durable response using the BRAF inhibitor vemurafenib in an EMM patient harboring the BRAF V600E mutation [16]. Recently, immune therapies using autologous T cells expressing a tumor-specific chimeric antigen receptor have also shown promising responses (including a complete response) in relapsed EM patients [17]. For CNS EM, the combination of CNS radiotherapy, IT chemotherapy, and systemic IMiD based therapy is strongly recommended [3].

At the time of relapse, previous lines of therapy and the duration of response should be taken into account. There is no rationale to favor a specific therapeutic class (eg, IMiD, PI, or monoclonal antibody) over another [3]. Pomalidomide has demonstrated a response rate of ~30% in EMM relapse [18]. The efficacy of, daratumumab and elotuzumab in EM has not been reported so far [3].

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