Research progress on treatment of extramedullary multiple myeloma

Yue Chen, a Shandong Tao, a Xinqi Zheng, a Yuye Shì, a Lijuan Zhang, a Kankan Chen, a Zhengmei He, a Chunling Wang, a,b and Liang Yu a,b

aDepartment of Hematology, The Affiliated Huaian No.1 People’s Hospital of Nanjing Medical University, Huai’nan, People’s Republic of China; bKey Laboratory of Hematology, Nanjing Medical University, Nanjing, People’s Republic of China

ABSTRACT

Objectives: Extramedullary multiple myeloma (EMM) is a relatively less frequent subentity of multiple myeloma (MM) and is generally considered to be a poor prognostic factor. Novel agents and hematopoietic stem cell transplantation (HSCT) have led to a significant improvement in the progression-free survival and overall survival of patients with MM, but outcomes of EMM remain dismal. Little is known regarding the role of novel therapies in this setting. This review summarizes the current available data regarding the roles of proteasome inhibitors, immunomodulators, monoclonal antibodies, chimeric antigen receptor (CAR)-T cell therapy and HSCT in EMM.

Methods: A systematic literature review through PubMed was conducted to summarize the published evidence on the therapeutic developments of novel agents and HSCT in EMM. Literature sources published in English were searched, using the terms multiple myeloma, extramedullary and treatment.

Results: Long-term outcomes of EMM patients remain dismal despite the utilization of novel agents and HSCT. The standard therapy of EMM has not been established. EMM should be managed as high-risk disease and treated accordingly.

Discussion and conclusion: This review will provide an insight on the current and emerging treatment strategies as well as their efficacy in EMM. Further subgroup analyses in large prospective trials focusing on EMM is needed to help optimize the therapy.

Introduction

Multiple myeloma (MM) is a plasma cell malignancy characterized by hypercalcemia, renal impairment, anemia, bone destruction, and immunodeficiency with recurrent infections due to accumulation of clonal plasma cells in the bone marrow (BM) and para-proteinemia [1]. Occasionally, myeloma cells may escape the BM niche resulting in extramedullary disease (EMD), namely extramedullary multiple myeloma (EMM), which may be present at MM diagnosis (primary EMM) or at the time of MM relapse (secondary EMM). EMM could be further divided into two types: (a) tumor masses develop via disruption of cortical bone and grow directly into adjacent tissue, that is EMB (bone-related) or also known as paramedullary, because it is not truly independent from bone lesions; (b) soft tissue masses invaded into extraneous locations from hematogenous spread, with no relationship to the bone and is referred to as EMS (soft tissue-related) [2–4]. It is of great importance to discriminate between the two types, as the latter is associated with worse outcome [3,5]. However, the majority of studies do not classify the types of EMM precisely and there is a trend to consider the form of EMS as the true EMM [6–8].

Diagnosis of EMM is typically made by imaging methods (ultrasound, computed tomography [CT], positron emission tomography [PET]/CT or magnetic resonance [MRI]) or physical examination. Conventional skeletal survey is acceptable under certain circumstances but not very sensitive in assessing EMM and should be replaced by better imaging [9]. Ultrasound can be performed in patients suspected of hepatic lesions or soft tissue infiltration [3]. Low-dose CT was reported to show the ability to detect extramedullary lesions. However, it does not offer functional information and the sensitivity is limited when lack of bone structure disruption [11]. As a technology possessing morphologic assessment and functional assessment of metabolic activity in focal lesions.
simultaneously, PET/CT is widely regarded as the modality of choice for EMM diagnosis [9,12]. Besides, PET/CT has a more established role over other imaging methods in distinguishing malignancies other than myeloma. MRI is also highly sensitive for imaging of EMM, especially functional MRI techniques. In a retrospective study comparing whole-body diffusion-weighted imaging (WB DWI) versus PET/CT in detecting intramedullary and extramedullary lesions in MM, WB DWI exhibited sensitivity equivalent to that of PET/CT with respect to identification of extramedullary lesions [13]. In case of clinical suspicion of EMM, imaging by either whole-body MRI or PET/CT is necessary to get precise data of EMB or EMS, both at diagnosis and relapse. Notably, biopsies should be performed wherever possible, as the findings of imaging might be false negative, and also to exclude other malignancies.

The incidence of primary EMB reported in observational studies varies from 7% to 34.2% [2,10], while primary EMS is less frequent and ranges from 1.7% to 4.5% [6,7,14]. According to the recent data from European Society for Blood and Marrow Transplantation (EBMT), the overall incidence of primary EMM was 18.2% (n = 682) and increased per year from 6.5% (2005) to 23.7% (2014) [15]. The precise incidence of secondary EMM remains unclear, ranging from 7.5% to 24–30% [3,6,15,16]. Table 1 summarizes the incidence of EMM in selected available studies. Interestingly, rates are also considered to be higher after invasive procedures (surgery or catheter insertion) or bone fracture [2,17,18]. Worth of note, extramedullary involvement had a peak incidence of 32–35% in relapsed cases after allogeneic stem cell transplantation (allo-SCT) [19,20]. However, the results should be interpreted with caution as allo-SCT is usually offered to very high-risk patients, while autologous stem cell transplantation (ASCT) is the upfront standard treatment for all fit MM patients. Therefore, the actual incidence of EMM after allo-SCT versus ASCT should be explored in comparable groups of patients, ideally in the context of prospective trials. Though it has also been doubted that rates of extramedullary progression are higher in patients exposed to novel agents [21], recent studies demonstrate that the administration of proteasome inhibitors (PIs) together with immunomodulatory drugs (IMiDs) did not result in an increase of EMM development, compared with conventional chemotherapy [6,10,22]. Moreover, the employment of lenalidomide before allogeneic transplantation was found to be associated with a reduced risk for extramedullary relapse [23].

EMM is a special clinical subentity and almost uniformly reported to be associated with a significantly shorter survival due to resistance to conventional treatments especially when occurring at relapse [3,4,6,7]. Multivariate analysis revealed that EMM patients tend to present with high-risk gene expression profile, high-risk cytogenetics, increased LDH level, as well as low hemoglobin and platelets levels [3,7,10]. Hence, in the opinion of some experts, EMM should be considered as high-risk MM and treated correspondingly [4,24]. In a longitudinal study on 1003 consecutive patients aimed to assess the prognostic impact of extramedullary myeloma involvement, 7% (76 of 1003) patients had primary EMM and 6% (56 of 1003) developed EMM during follow-up. Patients presented with EMM experienced a significantly worse progression-free survival (PFS) when compared with those without EMM (18 vs. 30 months, respectively). Moreover, the occurrence of EMM at any time in the course of the disease was related to shorter overall survival (OS) and PFS [10]. Similarly, another study focused on biological features and clinical outcomes of EMM got a similar conclusion, the 5-year OS and PFS were significantly shorter in patients with EMM than in non-EMM patients (31% vs. 59% and 21% vs. 50%, respectively) [7]. Pour et al. [3] also reported pronounced shorter OS for EMM patients compared to patients without EMM (38 vs. 109 months). Moreover, patients in EMS group had significantly inferior survival in comparison to EMB group (30 vs. 45 months), in line with previous reports [3]. Recently, an investigation on EMM by Gagelmann et al. [15] revealed that 3-year OS for patients with EMB was similar to classic MM patients (77.7% vs. 80.1%). While for those with EMS, the 3-year OS was significantly shorter (58%). Furthermore, many patients with EMM had more than one extramedullary sites, and multiple organ sites were associated with inferior outcome. In general, previous data indicate that EMM is an aggressive disease and associated with poor outcome (as reviewed in Table 1). Patients experiencing an extramedullary relapse have an even worse prognosis with an OS less than 6 months [3,25].

Remarkable progress has been made in myeloma treatment due to the integration of PIs, IMiDs and more recently monoclonal antibodies and chimeric antigen receptor (CAR)-T cell therapy. However, given the relative rarity of EMM, there are no randomized clinical trials to guide therapy in this setting and current experience regarding EMM treatment is mostly derived from retrospective studies (Table 1), the standard regimen has not been established. In the following parts, we will discuss the current and emerging treatment strategies as well as their efficacy in this clinical entity, with a focus on the role of PIs, IMiDs, monoclonal antibodies, CAR-T cell therapy and hematopoietic stem cell transplantation (HSCT).

PIs

PIs are considered as the key components of most regimens administered in MM patients. However, they are
| No. of MM patients | EMM incidence and classification | Therapy | PFS (EMM vs. MM) | OS (EMM vs. MM) | Author and Ref. |
|-------------------|-------------------------------|---------|-----------------|-----------------|----------------|
| 226              | 10% secondary EMB 14% secondary EMS | Conventional chemotherapy, novel agents, ASCT | Median time to progression after EMM relapse (5.4 months) | Median OS (38 vs. 109 months) | Pour et al. [3] |
| 174              | 7.5% primary EMS 3% secondary EMS | Pomalidomide plus low-dose dexamethasone within a phase II clinical trial | Not provided | Median OS (16 months vs. not reached) | Short et al. [6] |
| 3744             | 14.5% primary EMB 3.7% primary EMS | All patients received an upfront single ASCT within 12 months of diagnosis or a tandem ASCT within 6 months from first ASCT as first line therapy | EMB: 3-year PFS (50% vs. 47.9%) EMS: 3-year PFS (39.9% vs. 47.9%) | EMB: 3-year OS (77.7% vs. 80.1%) EMS: 3-year OS (58% vs. 80.1%) | Gagelmann et al. [15] |
| 117              | 32.5% primary EMB 1.7% primary EMS 27.4% secondary EMB 16.2% secondary EMS | Eight clinical trials of first line treatment with bortezomib-based regimens, with or without lenalidomide | Median OS (16 months vs. not reached) | Median OS secondary EMM: 2.47 years secondary EMS: 0.9 years | Varga et al. [22] |
| 329              | 14% primary EMM 28% secondary EMM (36% EMB, 52% EMS, 12% both) | All patients received an upfront single ASCT within 12 months of diagnosis or a tandem ASCT within 6 months from first ASCT as first line therapy | EMB: 3-year PFS (50% vs. 47.9%) EMS: 3-year PFS (39.9% vs. 47.9%) | EMB: 3-year OS (77.7% vs. 80.1%) EMS: 3-year OS (58% vs. 80.1%) | Gagelmann et al. [15] |
| 2332             | 11.4% primary EMM (91% EMB, 4.5% EMS, 4.5% not classified) | Three trials enrolled transplant eligible and five trials transplant ineligible patients. Three trials included an IMiD, lenalidomide in almost all cases, three trials a PI, and four trials both. Six out of eight trials included maintenance | Median PFS (25.5 vs. 25.2 months) 5-year PFS (19% vs. 22%) | Median OS (63.5 vs. 79.9 months) 5-year OS (51% vs. 59%) | Montefusco et al. [54] |
| 1965             | Primary EMM: 2.41% in TT, 4.35% in non-TT, and 4.5% in non-protocol patients. Secondary EMM (5 years after ASCT): 3.43% in TT, 5.2% in non-TT, and 7.24% of non-protocol patients | ASCT within TT protocols, non-TT protocols, and non-protocol patients | Primary EMM: 5-year PFS (21% vs. 50%) | Primary EMM: 5-year OS (31% vs. 59%) | Usmani et al. [7] |
| 1003             | 7% primary EMM (85% EMB and 15% EMS), 6% secondary EMM | Conventional chemotherapy (1971–1993), high-dose therapy for younger patients (1994–1999) and novel agents (2000–2007) | Median PFS (18 vs. 30 months) | Median OS (36 vs. 43 months) | Varettoni et al. [10] |
| 70               | 14.3% secondary EMM (after transplants) | ASCT-allo-SCT or allo-SCT with reduced-intensity conditioning | NA | NA | Perez-Simon et al. [19] |
| 172              | 20.4% secondary EMM (after transplants) | Sequential ASCT-allo-SCT. EMM were treated with donor lymphocyte infusion, radiotherapy, or chemotherapy, especially with novel agents | Median PFS did not differ significantly between patients with and without EMM at relapse | Median OS did not differ significantly between patients with and without EMM at relapse | Minnema et al. [20] |
| 271              | 16.2% primary EMM (after transplants) | Induction regimen using novel agents, VAD, or alkylating agents. All patients underwent ASCT | Median PFS (18 vs. 44 months) | Median OS (32 vs. 100 months) | Kumar et al. [67] |
| 663              | 1.2% primary EMS 6.3% secondary EMS 0.8% primary and secondary EMS (after transplants) | All 55 EMS patients received a median of 4 different treatment regimens prior to the development of EMS. All underwent ASCT and 15 also underwent allo-SCT | Median PFS from EMM diagnosis was 1.3 years | Median OS from EMM diagnosis was 1.3 years | Weinstock et al. [14] |
| 488 (No. of EMM) | 77% primary EMB 18% primary EMS 5% both | All 488 EMM patients received induction regimen with or without bortezomib. All patients underwent first line ASCT, tandem ASCT or auto-allogeneic transplant | 4-year PFS first line ASCT: 43% tandem ASCT: 52% auto-allogeneic transplant: 58% | 4-year OS first line ASCT: 70% tandem ASCT: 83% auto-allogeneic transplant: 88% | Gagelmann et al. [68] |
| 226 (No. of EMM) | 57.5% primary EMM (29.2% EMB and 70.8% EMS) 42.5% secondary EMM (12.5% EMB and 87.5% EMS) | Initial therapy with IMiD-based or PI-based regimens followed by ASCT | Median PFS: primary EMM 51.7 months primary EMS 38.9 months secondary EMM 20.9 months secondary EMS 13.6 months | Median OS: primary EMM not reached primary EMS 46.5 months secondary EMM 39.8 months secondary EMS 11.4 months | Beksac et al. [69] |
not indispensable along with the advances in MM therapy. For example, in two recent important clinical trials – MAIA trial for newly diagnosed MM and APOLO trial for relapsed/refractory MM (R/RMM), PIs were not included in the treatment strategy [26,27]. Three representative agents in this class have been approved by FDA – the reversible first-in-class drug bortezomib, the irreversible second-generation agent carfilzomib, and the first orally available PI, ixazomib. Additionally, three other PIs are currently under investigation in clinical trials, including marizomib, oprozomib and delanzomib [28].

Studies have demonstrated the anti-tumoral activity of bortezomib in EMM patients [29–31]. A previous study evaluating the survival outcomes according to the presence of primary EMM found that the adverse impact of EMM observed in transplant-ineligible patients was weakened among those treated with bortezomib-based regimen, highlighting the potential benefit of bortezomib in transplant-ineligible patients with primary EMM [32]. Recently, Lakshman et al. [33] investigated the efficacy of VDT-PACE (bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide)-like regimens in 141 R/RMM patients, of which 36% (51 of 141) had an extramedullary invasion. The overall response rate (ORR) did not differ significantly between the patients with or without EMM (57.1% vs. 52.9%), indicating that this combination regimen might partly abrogate the negative effect of EMD in R/RMM patients, in line with the recommendation of VDT-PACE for EMM from the Mayo Clinic guideline [34]. However, this regimen could be difficult to tolerate due to high incidence of treatment-related adverse events including myelosuppression, neuropathy, and thrombotic events, which consequently limits its wide clinical application [35,36].

The second-generation PIs in EMM is not fully elucidated and mostly focus on carfilzomib. Carfilzomib combined with lenalidomide and dexamethasone appears to be effective in high-risk myeloma patients and is considered as a preferred regimen for such specific situation [37]. Moreover, the effectiveness of carfilzomib in high molecular risk patients is also confirmed in ENDEAVOR study [38] and ASPIRE study [39]. Based on the above evidence, it is reasonable to speculate that carfilzomib may also work in the EMM setting. In a multicenter retrospective study evaluating carfilzomib monotherapy or in combination with other agents as salvage treatment for R/RMM, the presence of EMM (23.7%, 32 of 135) led to a strong trend towards reduced clinical benefit response (CBR) compared to those without EMM (43.3% vs. 63.5%). Similarly, the duration of response was also shorter in EMM patients compared to non-EMM patients (3.9 vs. 9.3 months). However, when considering ORR, the difference did not reach statistical significance between the two groups [40]. In a single myeloma case with pleuropericardial involvement, a quick and durable complete response (CR) was observed by Espanol et al. [41] after carfilzomib and dexamethasone combination therapy. Quite recently, Xiang Zhou et al. [42] retrospectively analyzed the role of carfilzomib in 45 patients with extramedullary R/RMM, including 20 (44%) with EMB and 25 (56%) with EMS. In total, a serological ORR of 59% and CBR of 83% were observed. With regard to extramedullary response, 9 of 33 evaluable patients achieved partial response (PR) (ORR = 27%) and the CBR was 54%. The median PFS and OS were five and ten months, respectively. EMS was associated with a significantly inferior PFS and OS compared to EMB. Of note, no extramedullary response was observed in 15 (33%) patients despite serological response, highlighting the importance of evaluating the imaging response in extramedullary sites.

In summary, PIs especially carfilzomib has shown some efficacy in EMM patients, but whether it could overcome the negative prognostic value of EMM needs further investigation.

**IMiDs**

Thalidomide was the first drug in the class of IMiDs that was found to have clinical activity against MM. However, its use often relates with significant adverse effect, particularly in older patients. Hence, another two thalidomide analogs with more potent anti-myeloma effects were developed and approved by FDA for the treatment of MM patients – lenalidomide and pomalidomide, which are now considered as the leading examples of IMiDs and administered widely in clinical.

According to the consensus statement of the International Myeloma Working Group (IMWG), thalidomide does not abolish the adverse effect of high-risk features [43]. The efficacy of this agent on EMM was conflicted. Although a report by Biagi et al. [44] described three patients with extramedullary relapse following allogeneic BM transplantation attained CR after thalidomide therapy, other groups observed poor effect of this drug [2,45,46].

In contrast, lenalidomide, as well as pomalidomide, seem to be more effective in the EMM setting. Calvo Villas et al. [47] reported the lenalidomide containing regimens in 18 patients with advanced and extramedullary MM, 11 patients (61.1%) achieved varying degrees of response in the EMD, including complete disappearance in eight patients (44.4%) and decrease in size in three patients (16.6%), indicating that lenalidomide could be effective in R/RMM with EMD, similar to the previous observations [48,49]. Of note, three responding patients relapsed shortly, suggesting lenalidomide-based therapy need further improvement to
enhance the control of the disease. Chisako et al. [50] presented two EMM cases successfully treated with lenalidomide and dexamethasone who were resistant to bortezomib therapy. Marked reduction in the size of extramedullary masses was found in both of them, suggesting lenalidomide could be considered as a potent treatment option for bortezomib-resistant refractory EMM patients. Additionally, lenalidomide combined with donor lymphocyte infusions (DLI) has also shown particular effectiveness with a 62% response rate in patients with extramedullary relapse after allo-SCT [23].

In a phase II clinical trial of pomalidomide plus low-dose dexamethasone, EMD was present in 7.5% (13 of 174) of R/RMM patients. The response rate of EMM to pomalidomide and low-dose dexamethasone was 31% (4 of 13), including two CR and two PR [6]. Another multicenter retrospective study investigated 127 patients treated with novel agents for EMM relapse and the central nervous system (CNS) as their single EMD site was excluded. The ORR was 57%, IMiDs were found to provide a higher ORR when compared with PIs and chemotherapy. And the administration of IMiDs-based therapy followed by autologous transplantation appeared to be beneficial in delaying the development of EMM relapse [51].

Recently, the efficacy of pomalidomide-cyclophosphamide-dexamethasone regimen in seven R/RMM patients with EMD was retrospectively evaluated by a Japanese group. Three of the seven patients achieved very good partial response (VGPR) and no severe infections occurred during the treatment period. In addition, a patient complicated with secondary plasma cell leukemia obviously improved with the combination therapy and succeeded to ASCT [52]. Of note, pomalidomide crosses the blood-brain barrier while lenalidomide does not. Pomalidomide-based regimen has also shown effectiveness in CNS myeloma. Mussetti et al. once reported a case relapsed to bortezomib therapy. Marked reduction in the size of extramedullary lesion and M protein gradually disappeared in 2 months after CAR-T treatment, the tumor in the liver disappeared. However, the responses were not durable, both patients progressed shortly with extramedullary lesions at new sites along with intramedullary relapse.

On the basis of data from a meta-analysis consisting of eight trials (three enrolled for transplant eligible and five for transplant ineligible), EMM patients (11.4%, 267 of 2332) receiving IMiDs, mainly lenalidomide, or PIs yielded similar PFS when compared with classical MM patients, denoting that the presence of EMM at diagnosis had limited detrimental effect in patients treated with novel agents [54]. Conversely, another group came to a different conclusion about IMiDs. No responses were noted among extramedullary R/RMM patients treated with pomalidomide-dexamethasone [55]. Hence, larger studies are required to investigate the effectiveness of IMiD (mainly lenalidomide and pomalidomide) based regimen in EMM patients.

### CAR-T cell therapy

In recent years, immune therapies using CAR T cells have brought new hopes in treating hematological malignancies, including MM. CAR-T cell therapy is already approved by FDA and EMA for R/R B-acute lymphoblastic leukemia (B-ALL), diffuse large B-cell lymphoma (DLBCL) [56,57] and this year for RRMM [58], yet we do not have real world data in myeloma since only recently approved. The commonly used targets in MM are kappa light chain [59], CD19 [60], and B-cell maturation antigen (BCMA) [61,62], of which BCMA is considered as the most appealing and widely tested target [63].

Regarding the effect of CAR-T cell therapy on EMM, very few reports (limited by very low number of patients) were published. However, its encouraging anti-myeloma clinical activity has been demonstrated by the promising responses (including CR) in relapsed EMM patients. The first-in-humans clinical trial of BCMA-CAR-T therapy in 16 MM patients demonstrated that CAR-BCMA T-cell had encouraging activity against R/RMM, the ORR was 81%, with 10 of 16 (63%) achieving VGPR or CR. Furthermore, responses include eradication of soft-tissue extramedullary plasmacytoma. One patient had a large left abdominal mass before CAR-T treatment, the tumor reduced markedly in size 4 weeks post infusion and was undetectable on CT imaging 55 weeks after CAR-T administration [62].

Recently, Jie Xu et al. [64] conducted a clinical trial of a biepitope-targeting CAR T against BCMA (LCAR-B38M) in a series of 17 R/RMM cases, a high ORR of 88.2% was achieved, including 13 stringent complete response (sCR) and 2 VGPR. Notably, CAR T therapy also exhibited encouraging therapeutic effects in patients with extramedullary lesions. Patient RJ02 bore plasmacytoma on the forehead, the tumor was resistant to three lines of anti-MM drugs and enlarged gradually, lasting for nearly 3 years. The initial treatment response to CAR-T cell therapy was PR with negative minimal residual disease (MRD) in the BM. Four months later, the extramedullary lesion and M protein gradually disappeared to reach an sCR. Another patient RJ03 had multiple plasmacytomas with skin, lower jaw, and liver involvement, a negative BM MRD was obtained quickly. The lesions on the skin eliminated at day 19 post CAR T infusion, and the mass in the lower jaw reduced obviously under the skull MRI scan. Six months after CAR-T therapy, the tumor in the liver disappeared. However, the responses were not durable, both patients progressed shortly with extramedullary lesions at new sites along with intramedullary relapse.

Overall, CAR-T therapy has shown promising results in EMM patients, but a longer time of follow-up is
needed to further evaluate the real outcome of this approach.

**HSCT**

The prognosis of patients with MM, particularly R/RMM, has been improved significantly over the past decade with the development of HSCT. However, given the relative infrequency of EMM, limited data are available on their outcome following HSCT.

**ASCT**

Several studies suggest that patients with EMM may benefit from early ASCT [32,65,66], yet most studies consistently reveal a poor outcome despite the administration of ASCT (Table 1). A comparative study analyzed 271 consecutive ASCT recipients of MM patients, of which 44 (16.2%) with EMM at diagnosis [67]. Similar to earlier reports [7,14], the CR rate, median PFS and OS were significantly lower for patients with EMM compared to non-EMM, suggesting that ASCT had limited effects on improving the prognosis of EMM. Until now, investigations on the efficacy of tandem ASCT in such a special group of patients are limited. The study registered in EBMT by Gagelmann et al. [15] evaluated the impact of EMM on the outcome after upfront single (n = 124) or tandem ASCT (n = 15) as first-line therapy. The results showed that there was no significant difference of 3-year OS and PFS between tandem and single ASCT (OS was 52.0% for tandem ASCT vs. 64.9% for single ASCT and corresponding PFS was 56.2% vs. 48.3%, respectively), suggesting that double ASCT did not bear the superiority in improving the prognosis of patients with EMM when compared with single ASCT. Contrarily, in another study by Gagelmann et al., outcome of patients with EMM (41% of which had at least 1 high-risk cytogenetics) receiving single ASCT (n = 373) as well as tandem ASCT (n = 84) were compared. OS and PFS were 70% and 43% for single ASCT vs. 83% and 52% for tandem ASCT (p = .06 and p = .30). For EMM patients, tandem ASCT was significantly associated with better outcome vs. single ASCT in multivariable analysis [68]. Very recently, in a multicenter retrospective study from 11 countries, a total of 100 patients with EMM underwent ASCT, of which 67 (51.5%) with primary EMM. Front-line ASCT demonstrated a survival advantage for EMM patients. Among those who received ASCT, the median PFS was 49 months and for those who did not receive ASCT the median PFS was merely 28.1 months (p < 0.001). Depth of response (achieving VGPR or not) after ASCT did not affect PFS [69].

**Allo-SCT**

Allo-SCT, although a potentially curative treatment, is not yet defined in MM and it is not regarded as a standard therapy by most experts in the field [70]. The effect of allo-SCT on EMM is dubious. Moreover, some studies even suggest a higher incidence of EMM after allo-SCT [19,20]. In a retrospective analysis including 33 patients with EMM, significantly shorter PFS (median, 3 months) and OS (median, 8 months) were observed even after allo-SCT compared to patients without EMM. Nevertheless, a plateau at 25% survival indicated allo-SCT might induce long-term remission in EMM patients including those with del17p or multiorgan involvement [71], which is very promising results even in the time of new agents era. Collectively, the role of HSCT (single/tandem ASCT or allo-SCT) for patients with EMM remains to be debated and need more study.

**Monoclonal antibodies**

Monoclonal antibodies are an emerging class of agents in MM, targeting cell surface tumor antigens such as CD38 and SLAMF7 (also known as CS-1 or CD319), with more on-target and less off-tumor effects.

Daratumumab (DARA), the first human anti-CD38 IgG1 monoclonal antibody, was approved by FDA and EMA for treatment of newly diagnosed and relapsed MM due to its anti-tumor efficacy through pleiotropic mechanisms, including complement-dependent cytotoxicity (CDC) [72], antibody-dependent cellular cytotoxicity (ADCC) [72], antibody-dependent cellular phagocytosis (ADCP) [73], induction of direct apoptosis [74], and immunomodulatory effects [75]. Another antibody approved for the use in MM is elotuzumab, a humanized IgG1 antibody targeting SLAMF7. The introduction of daratumumab and elotuzumab in combination with bortezomib or IMiDs has significantly improved the prognosis of patients with R/RMM. Moreover, daratumumab monotherapy yielded encouraging activity in heavily pretreated and highly refractory MM patients, whereas elotuzumab lacked the single-agent efficacy. So far, there are only limited reports on experience regarding the efficacy of daratumumab and elotuzumab in EMM, either as single agent or in combination.

The study conducted by Lonial et al. [76] suggested a potential activity of daratumumab in patients with EMM. In the study, 14 of 106 (13%) MM patients were previously treated with at least three lines of therapy and had more than one extramedullary plasmacytoma. Overall responses occurred in 3 of 14 patients (21.4%) after daratumumab monotherapy. Similar results were reported in a real-life study of MM patients receiving single-agent daratumumab in the Czech Republic [77]. A pooled analysis of 2 phase I/II trials by Usmani
et al. [78] evaluated the efficacy and safety profiles of daratumumab monotherapy in heavily pretreated 148 R/RMM patients, with 18 (12%) had at least one extra-medullary plasmacytoma. The ORR was 33.1%, including 26 PRs, 13 VGPRs, 4 CRs, and 3 SCRs. For patients with EMM, the ORR was 16.7%. Pick et al. [79] reported a retrospective analysis involving 30 heavily pretreated advanced-stage MM patients in a single center receiving daratumumab-based therapy. An ORR of 36% was obtained, with a short median PFS and OS of 2.3 and 6.6 months, respectively. Only 2 of 9 patients with EMM achieved PR and both progressed shortly (50 and 85 days) after treatment initiation.

Very recently, the first report of the effectiveness of elotuzumab for EMM was described by Kashima et al. [80] in a heavily pretreated MM patient resistant to combination regimens of pomalidomide-dexamethasone, daratumumab-lenalidomide-dexamethasone, and ixazomib-lenalidomide-dexamethasone. ELD (elotuzumab-lenalidomide-dexamethasone) regimen was administered following 3 cycles of short VAD (vincristine, doxorubicin, and dexamethasone). After 8 cycles of ELD, the EMD disappeared, suggesting the potential efficacy of elotuzumab in EMM setting.

Taken together, daratumumab and elotuzumab may offer another approach of targeted therapy in this special entity. However, this finding needs to be further evaluated by larger studies.

**Conclusion**

EMM is a relatively less frequent clinical condition of MM and may occur at any time during the course of the disease. Our knowledge regarding EMM is limited and mostly derives from retrospective studies. In our opinion, it would be markedly beneficial if EMM could be described by the same abbreviations in all studies and classified precisely whether the tumor is extending from the bone or soft tissues in extramedullary locations, since the prognosis of the two types differs significantly. Besides, imaging guidelines need to be established for better diagnosis and assessment of EMM. Despite the administration of new agents and HSCT, long-term outcomes of EMM patients remain dismal, and how to further improve the outcome of this special clinical entity remains a great challenge. Overall, experts agree in managing EMM as high-risk disease and treating accordingly. Based on the guidelines from the Mayo Clinic for EMM, the use of combination therapy with VDT-PACE was recommended to EMM patients, and the response was better consolidated with ASCT or allo-SCT for fit patients if possible. While for frail patients, a daratumumab- or anthracycline-based regimen is favorable [35]. Moreover, radiotherapy for soft-tissue plasmacytoma should be taken into consideration to improve local disease control and analgesia [4]. From the limited recent literature, the next-generation PIIs, IMiDs, or the monoclonal antibodies, CAR-T cell therapy seems to be efficacious in this setting, but the rarity of this disease and the lack of prospective trials make it difficult to generate solid data. In the future, subgroup analyses in large prospective trials focusing on EMM is highly recommended to help define the optimal strategy.

**Disclosure statement**

The authors have no competing interest.

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