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INVITED REVIEW

Myeloma bone disease: pathogenesis and management in the era of new anti-myeloma agents

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Abstract

Introduction Multiple myeloma (MM) is a malignancy of plasma cells with characteristic bone disease. Despite recent great strides achieved in MM treatment owing to the implementation of new anti-MM agents, MM is still incurable and bone destruction remains a serious unmet issue in patients with MM.

Approach In this review, we will summarize and discuss the mechanisms of the formation of bone disease in MM and the available preclinical and clinical evidence on the treatment for MM bone disease.

Conclusions MM cells produce a variety of cytokines to stimulate receptor activator of nuclear factor-κB ligand-mediated osteoclastogenesis and suppress osteoblastic differentiation from bone marrow stromal cells, leading to extensive bone destruction with rapid loss of bone. MM cells alter the microenvironment through bone destruction where they colonize, which in turn favors tumor growth and survival, thereby forming a vicious cycle between tumor progression and bone destruction. Denosumab or zoledronic acid is currently recommended to be administered at the start of treatment in newly diagnosed patients with MM with bone disease. Proteasome inhibitors and the anti-CD38 monoclonal antibody daratumumab have been demonstrated to exert bone-modifying activity in responders. Besides their anti-tumor activity, the effects of new anti-MM agents on bone metabolism should be more precisely analyzed in patients with MM. Because prognosis in patients with MM has been significantly improved owing to the implementation of new agents, the therapeutic impact of bone-modifying agents should be re-estimated in the era of these new agents.

Keywords Myeloma bone disease · Receptor activator of nuclear factor-κB ligand · Bone-modifying agents · Proteasome inhibitors · Daratumumab

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Introduction

Multiple myeloma (MM) is a malignancy of plasma cells. It has a unique propensity to almost exclusively develop in the bone marrow and generates devastating bone destruction with enhanced osteoclastic bone resorption and concomitant suppression of bone formation. MM arises from its precancerous stage, monoclonal gammopathy of unknown significance (MGUS). In parallel with the progression of MGUS into MM, microenvironmental changes occur in the bone marrow, including increased osteoclastogenesis and angiogenesis and impaired immune function. This pathologically skewed bone marrow microenvironment in turn stimulates MM cell growth and survival to cause drug resistance.

Bone disease is a characteristic feature of MM. Various novel anti-MM agents have been developed, and recent combination treatments among them are able to exert prompt and deeper response in a greater portion of patients with

relapsed/refractory MM as well as newly diagnosed MM. However, MM is still incurable and eventually relapses; and bone destruction after repeated relapses remains a serious unmet issue in patients with MM. This review summarizes the mechanisms of the formation of bone disease in MM and the available preclinical and clinical evidence on the treatment for MM bone disease.

Bone metabolism in MM

Imbalance between osteoclastogenesis and osteoblastogenesis in MM

Image-documented bone lesions are observed in 80–90% of patients with MM during the course of their disease progression; 40% are reported to experience pathological fractures within the first year after diagnosis [1]. Typical images of bone disease in patients with MM are shown in Fig. 1. The pain and immobility caused by bone fractures can significantly reduce the quality of life (QoL) of patients with MM and may negatively affect treatment outcomes and thereby their life expectancy. Therefore, early detection of bone lesion(s) and therapeutic intervention are important in the treatment of MM. Bone metabolic markers can indicate ongoing bone metabolism and are widely used for the diagnosis and monitoring in osteoporosis and other disorders of bone metabolism. Levels of the bone resorption marker urinary deoxypyridinoline are increased in the majority of patients with MM, while levels of the bone formation marker serum osteocalcin are relatively decreased [2, 3], suggesting an imbalance of bone turnover with enhanced osteoclastic bone resorption and concomitantly suppressed bone formation.

For osteoclastogenesis, the interaction between the receptor activator of nuclear factor-κB (RANK) and its ligand (RANKL) has been demonstrated to play a vital role. The expression of RANKL is induced in bone marrow stromal cells (BMSCs)/osteoblasts by various cytokines and physiologically active substances. Binding of RANK to RANKL stimulates osteoclastic differentiation and activation. Osteoprotegerin (OPG), a decoy receptor for RANKL, inhibits the binding of RANK to RANKL. OPG is produced from various types of cells, including T cells, megakaryocytes, and BMSCs/osteoblasts. These factors are also produced by osteocytes embedded in the bone matrix. Thus, the balance of RANKL expression and OPG production in the bone marrow determines the levels of osteoclastogenesis. In bone specimens from normal subjects, RANKL expression is low, but OPG expression is relatively high [4]. However, in those patients with MM, RANKL expression is increased in BMSCs, whereas OPG production is suppressed, indicating the predominance of RANKL activity in the MM bone marrow microenvironment.

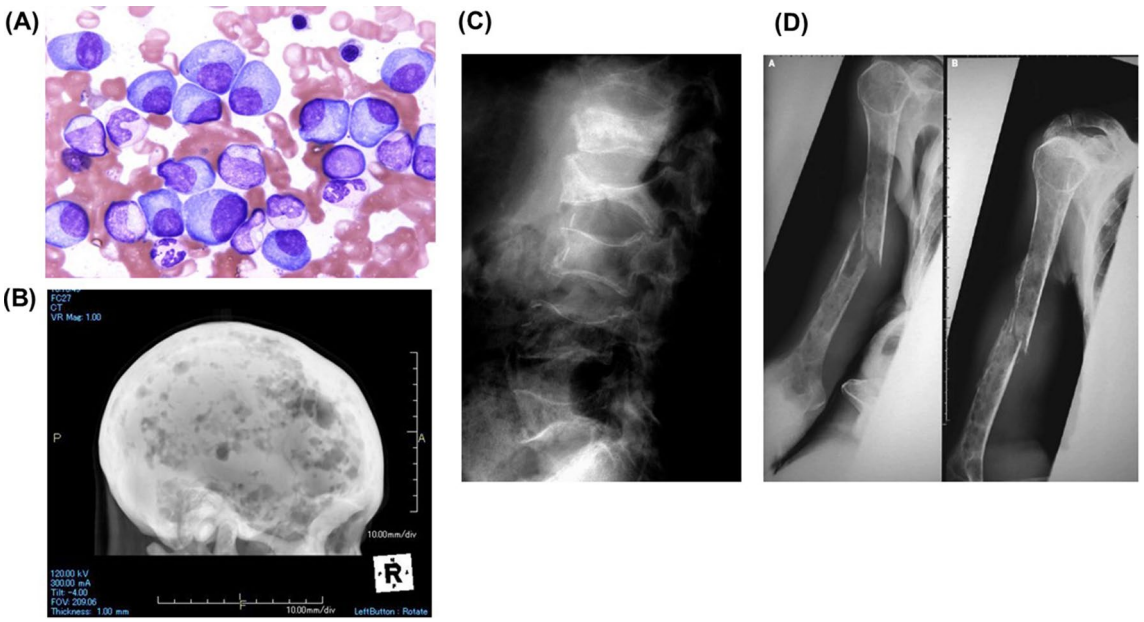

Fig. 1 Images of bone disease in patients with MM. **A** Myeloma tumor cells accumulate in the bone marrow. **B** Multiple compression fractures in lumbar vertebrae. **C** Multiple radiolucent lesions without ossification, known as "punched-out lesions" in a skull X-p, implying enhanced bone resorption along with impaired calcification. **D** Bone fractures in long bone occur in an advanced case

Pathogenic factors and clinically relevant biomarkers for MM bone disease

Cytokines aberrantly over-produced by MM cells, including macrophage inflammatory protein (MIP)-1α and interleukin (IL)-34 as well as MM cell adhesion up-regulate RANKL in BMSCs, which play a major role in the enhancement of osteoclastogenesis and bone resorption in MM [5–7]. In addition, factors over-produced by MM cells and/or their surrounding microenvironment in bone such as soluble Wnt inhibitors, IL-3, IL-7, tumor necrosis factor alfa (TNF-α), activin A, and transforming growth factor beta (TGF-β) have been demonstrated to suppress osteoblastic differentiation [8–13]. Therefore, multiple factors act together to eventually develop extensive bone destruction in MM (Fig. 2). These factors can be utilized as clinical biomarkers to detect bone disease and evaluate its severity. Some of them have been reported as follows:

Soluble RANKL

Serum levels of soluble RANKL (sRANKL) and OPG and sRANKL/OPG ratios have been reported to be indicators of osteoclastic activity in patients with MM [14]. The serum sRANKL/OPG ratios increase and correlate with the clinical severity of bone destruction in patients with MM. They were also reported to have a negative impact on overall survival in patients with MM [14]. However, the impact of such factors on prognosis should be re-estimated, because prognosis in patients with MM has been significantly improved by new anti-MM agents.

Macrophage inflammatory protein-1

MM cells from patients with multiple bone lesions secreted significantly higher amounts of MIP-1α and MIP-1β than those from patients with less advanced bone disease [7], suggesting the correlation between MM cell ability to produce MIP-1 and clinical severity of the bone disease. MIP-1α and MIP-1β as well as cocultures of MM cells enhanced in vitro osteoclast formation and activation from bone marrow cells. MIP-1α and MIP-1β induced RANKL expression in BMSCs in the presence of a physiologically low concentration of 1,25-dihydroxyvitamin D3. Addition of a surplus of OPG was able to inhibit RANKL activity and the effects of MIP-1α and MIP-1β and by MM cells, indicating a critical role of RANKL in osteoclast differentiation and activation in MM. Serum levels of MIP-1α positively correlated with the values of bone resorption markers in patients with MM with bone lesions [15].

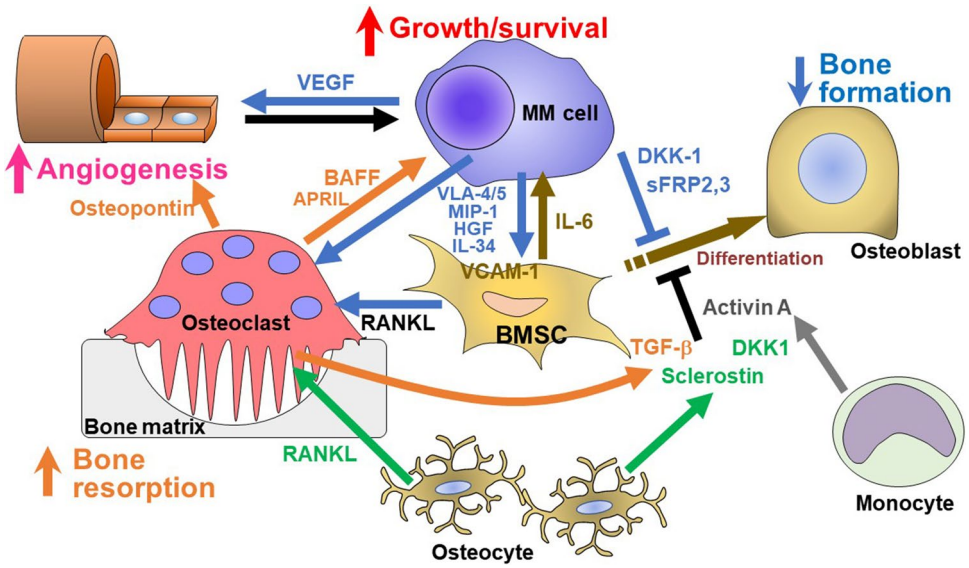

Fig. 2 Bone destruction by factors over-produced by MM cells and/or their surrounding microenvironment in bone in MM. MM cells enhance osteoclastogenesis and suppress osteoblastic differentiation from bone marrow stromal cells (BMSCs), leading to skewing of the cellular microenvironment in the bone marrow. Cytokines aberrantly over-produced by MM cells, including MIP-1, HGF and IL-34 as well as MM cell adhesion (VLA4/5-VCAM-1) up-regulate RANKL and IL-6 production in BMSCs to enhance osteoclastogenesis and MM cell growth/survival. Osteoclasts enhance MM cell growth/survival. MM cells enhance angiogenesis in concert with osteoclasts. In addition, factors over-produced by MM cells and/or their surrounding microenvironment in bone such as soluble Wnt inhibitors, IL-3, IL-7, TNF-α, activin A and TGF-β suppress osteoblastic differentiation. RANKL and sclerostin are over-produced by osteocytes. Therefore, multiple factors act together to eventually develop extensive bone destruction along with MM tumor expansion

Hepatocyte growth factor

Serum levels of hepatocyte growth factor (HGF) are elevated in patients with MM with osteolytic lesions compared with patients with MGUS or normal subjects, and HGF levels correlated with the extent of osteolytic lesions [16, 17]. HGF is produced by MM cells and the bone marrow microenvironment and exerts diverse actions, including MM cell survival, homing, bone remodeling, and angiogenesis [18]. HGF induces RANKL expression in BMSCs/osteoblasts to promote osteoclastogenesis and suppresses their Runx2 and Osterix expression to impair osteoblastic differentiation [19].

Soluble Wnt inhibitors

Wnt/β-catenin signaling is essential for osteoblast differentiation, which is negatively regulated by multiple soluble inhibitors. A series of secreted Frizzled-related proteins (sFRPs) and dickkopf (DKK) family members as well as sclerostin have been identified as soluble inhibitors for Wnt/β-catenin signaling [9, 20, 21]. DKK1 is produced by osteoblasts and osteocytes along with MM cells [21, 22]. Serum DKK1 levels are increased in patients with MM with bone disease and decreased as MM responds to anti-MM treatment [22, 23]. Sclerostin is a glycoprotein with a cystine knot-like domain that is almost exclusively expressed and produced by osteocytes [24]. Serum sclerostin levels are increased in patients with MM with bone lesions and correlate with clinical stages and the severity of bone destruction [13]. Sclerostin expression was found in BMSCs/osteoblasts in addition to osteocytes in biopsy specimens from bone lesions in patients with MM [25]. The underlying mechanisms for the over-production of sclerostin in MM bone lesions remain to be clarified.

Other soluble factors

TNF-α, IL-7, and IL-3 have also been reported as inhibitory factors of osteoblast differentiation derived from MM cells [26–28]. TGF-β specifically inhibits the terminal differentiation (calcification) of osteoblasts [10]. TGF-β is stored as a latent form in the bone matrix and released from the bone by osteoclastic bone resorption and becomes an active form by acids and enzymes produced by osteoclasts. In osteoclastic bone lesions, activated TGF-β is abundantly released from bone tissues to suppress calcification. Activin A, another TGF-β family cytokine, is also overproduced from the bone marrow microenvironment in MM to suppress osteoblastogenesis [12, 29, 30]. In addition, other factors, including LIGHT [31], semaphorin 4D [32], and IL-34 [33] have been reported to be associated with the progression of MM bone lesions. These factors may become potential biomarkers for bone disease in MM.

MicroRNAs

MicroRNAs are short RNAs with about 21 bases that are produced when long RNAs transcribed from DNA are processed by DROSHA and DICER. MM cells and cells surrounding them in the bone marrow secrete exosomes that contain a wide variety of microRNAs [34]. As a potential biomarker for bone lesions, Hao et al. reported that serum miR-124 levels were higher in patients with MM with bone lesions and correlated with the extent of bone lesions [35]. Targets of miR-124 include the PTEN gene, which is involved in skeletal and muscle metabolic regulation via PI3K/AKT [36]. miR-135b has been implicated to inhibit the bone morphogenetic protein (BMP)-Smad pathway, and its increased production correlates with the severity of bone lesions [37]. miR-21-5p increases the RANKL/OPG ratio in BMSCs in patients with MM [38], whereas miR-342-3p, miR-363-5p and miR-203a-3p suppress osteoblastogeneis through targeting the Runx2, BMP-Smad and canonical Wnt-β-catenin pathways [39, 40]. A number of microRNAs have been demonstrated to be associated with MM pathogenesis.

Mutual interaction between MM cells and bone microenvironment

MM niche

MM cells enhance osteoclastogenesis and suppress osteoblastic differentiation from BMSCs, leading to skewing of the cellular microenvironment in the bone marrow (Fig. 2). Angiogenesis is also enhanced through these cellular interactions. These cells surrounding MM cells create a cellular microenvironment suitable for MM cell growth and survival to confer drug resistance, which can be called an "MM niche".

Among cell components in the bone marrow in MM, the roles of BMSCs in MM cell growth and survival have been well studied. The interaction between MM cells and BMSCs confers MM cell homing, growth, survival, and resistance to chemotherapy [41]. MM cells stimulate BMSCs to produce various growth and anti-apoptotic factors for MM cells, including IL-6, IGF-1, SDF-1α, IL-21, B-cell-activating factor (BAFF), and vascular endothelial growth factor (VEGF) while inducing RANKL to enhance osteoclastogenesis. Notably, the adhesion of MM cells to BMSCs via VLA-4 and/or VLA-5 confers cell adhesion-mediated drug resistance (CAM-DR) in MM cells [42]. Autocrine activation of VLA-4 on MM cells by MM cell-derived MIP-1 and the up-regulation of MIP-1 production by MM cells through the VLA-4-VCAM-1 interaction appear to form a positive feedback loop between the adhesion of MM cells to BMSCs

and MIP-1 production by MM cells [43]. In addition to osteoclastogenesis, MIP-1 has been suggested to promote MM cell homing to or colonization in the bone marrow, which further enhances CAM-DR in MM cells.

In normal trabecular bones, bone remodeling with bone resorption by osteoclasts followed by bone formation by osteoblasts occurs in the bone remodeling compartments covered by canopy cells [44]. However, canopy cells disappear, and bone remodeling compartments are disrupted in MM [45], and MM cells go into the bone remodeling compartments and directly interact with osteoclasts and osteoblastic lineage cells. When MM cells are isolated from patients with MM and cultured alone, MM cells soon die [46]. However, MM cells are alive and proliferating in the presence of osteoclasts, indicating that osteoclasts are not mere bone-resorbing cells but they support MM cell growth and survival. MM cells enhance osteoclastogenesis, and osteoclasts produce multiple growth and survival factors for MM cells, including TNF family cytokines, BAFF and APRIL [47, 48], thereby forming a vicious cycle between osteoclastic bone destruction and MM tumor progression. Lawson MA, et al. demonstrated that RANKL-driven osteoclastogenesis stimulates MM cell proliferation and reduces the percentage of a dormant MM cell fraction in mouse MM models [49], suggesting that osteoclasts make dormant myeloma cells divide and proliferate.

The TGF-β–activated kinase 1-PIM2 pathway

To effectively kill MM cells residing within the MM niche and improve the efficacy of treatment against MM, we looked for novel molecules to be targeted through comprehensive analysis using a DNA microarray. We found that the serine/threonine kinase PIM2 is constitutively over-expressed, and further up-regulated in MM cells in cocultures with BMSCs as well as osteoclasts [50–52]. Hematological cancers highly express PIM2; and MM expresses PIM2 at the highest level among hematological malignancies [53]. PIM2 expression is increased in plasma cells in MGUS and much more in MM cells [54]. IL-6 and the TNF family cytokines BAFF and APRIL were found to play a predominant role in the PIM2 up-regulation in MM cells by interaction with BMSCs and osteoclasts. A variety of factors responsible for growth and survival signaling pathways in cancer cells are substrates of PIM kinases [55]; these PIM substrates regulate cellular processes critical for tumor progression and therapeutic resistance, making PIM a promising target for cancer therapy. Importantly, we reported that the PIM inhibitor SMI-16a dose-dependently suppresses the viability of MM cells. Treatment with the PIM inhibitor markedly suppressed the phosphorylation of 4E-BP1 to inhibit translation, and reduces Mcl-1 and c-Myc levels in MM cells [50]. Therefore, PIM2 acts as an important pro-survival mediator in MM cells in the bone marrow microenvironment, and is suggested to be an important therapeutic target in MM. Notably, PIM2 is also upregulated in BMSCs by MM cells as well as factors over-produced in MM bone lesions known to suppress osteoblastogenesis, suggesting PIM2 as a common downstream mediator of these inhibitory factors [51]. Enforced expression of PIM2 suppresses mineralized nodule formation or osteoblastogenesis by BMP-2, demonstrating PIM2 in BMSCs as a negative regulator for bone formation. RANKL enhances PIM2 expression in osteoclastic lineage cells during their osteoclastogenesis along with the induction of osteoclastic differentiation markers, c-fos, NFATc1, and cathepsin K [52]. The PIM inhibitor SMI-16a suppresses TRAP-positive osteoclast formation by RANKL.

We further looked into the molecular mechanism to upregulate PIM2 expression in MM cells and found the critical role of TGF-β–activated kinase 1 (TAK1) [56]. TAK1 inhibition reduced PIM2 expression along with suppression of the phosphorylation of 4E-BP1, a substrate of PIM2, in MM cells. TAK1 is constitutively overexpressed and phosphorylated in MM cell lines and primary MM cells from patients; and TAK1 inhibition suppresses the viability of MM cells. Cell–cell contact between MM cells and BMSCs via the VLA-4-VCAM-1 interaction is important for MM cell growth and drug resistance and osteoclastogenesis. VCAM-1 expression is upregulated in BMSCs when co-cultured with MM cells or cultured in the presence of TNF-α. However, TAK1 inhibition abrogates the upregulation of VCAM-1 expression, thereby suppressing MM cell adhesion to BMSCs and MM cell growth enhancement. Cocultures with MM cells enhance RANKL and IL-6 expression in BMSCs, which is also inhibited by TAK1 inhibition. Besides, TAK1 inhibition markedly suppressed the secretion of VEGF from MM cells. MM cell conditioned media as well as inhibitory factors for osteoblastogenesis overproduced in MM induce phosphorylation of TAK1 in BMSCs and suppress their osteoblastogenesis. In addition, RANKL-induced phosphorylation of TAK1 in preosteoclastic cells in parallel with degradation of IκB and nuclear localization of the NF-κB subunit p65 and phosphorylation of p38MAPK and ERK. Therefore, MM cells interact with BMSCs and osteoclasts in bone lesions to activate TAK1-mediated signaling in these cells to enhance MM tumor progression and osteoclastogenesis whereas suppressing osteoblastogenesis (Fig. 3). However, TAK1 inhibition directly and/or indirectly suppresses MM growth and resumes bone formation while suppressing osteoclastogenesis. Therefore, TAK1 inhibition may become a promising therapeutic option, targeting the interaction between MM cells and their surrounding microenvironment in MM bone lesions.

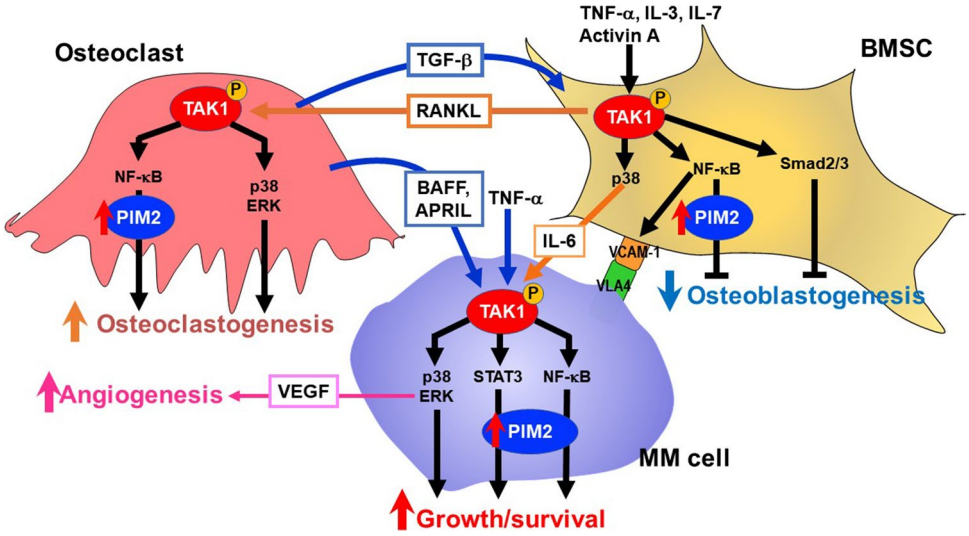

Fig. 3 The TAK1-PIM2 pathway in the mutual interaction between MM cells and the bone microenvironment. PIM2 is a novel pro-survival mediator for MM cells. Interaction with the MM bone marrow microenvironment potentiates PIM2 expression in MM cells through activation of the JAK2/STAT3 pathway by IL-6 and the NF-κB pathway by TNF family cytokines, TNF-α, BAFF, and APRIL, to promote MM cell growth and survival. At the same time, PIM2 is induced in osteoclasts and bone marrow stromal cells (BMSCs) though the interaction with MM cells to cause bone destruction. TAK1 is overexpressed and activated upstream of PIM2 in MM cells, BMSCs and osteoclasts through mutual interaction between these cells in the bone marrow. Besides PIM2 upregulation, TAK1 mediates a wide range of intracellular signaling pathways, including VEGF production via ERK in MM cells and the expression of VCAM-1 and RANKL in BMSCs. Therefore, TAK1 activation is vital for MM cell growth and survival and bone destruction

Osteocytes

Osteocytes are the most abundant cells in bone. Osteocytes are derived from osteoblasts and embedded in bone. Most osteoblasts undergo apoptosis after forming bone, but a portion of osteoblasts differentiate into osteocytes in the bone matrix [57, 58]. Osteocytes reside in the lacunae and connect with each other via their dendrites and sense and transmit mechanical signals via the lacuno-canalicular networks [59, 60]. In addition to being a sensor of mechanical stress, osteocytes act as a master regulatory cell of bone remodeling [61].

Under mechanical loading, the production of Wnt inhibitors sclerostin and DKK1 by osteocytes is decreased to increase bone formation [62, 63]. In contrast, mechanical unloading induces RANKL expression by osteocytes to enhance osteoclast formation and activity and thereby decreasing bone mass. Rummler et al. reported an interesting experiment with mechanical loading in MM animal models [64]. The knee and ankle were fixated and mechanical loading with repeated forced compression was applied to tibiae into which MM cells were inoculated. Bone resorption area was increased in MM cell-inoculated tibiae more than in non-loaded control mice. However, mechanical loading suppressed bone resorption and instead increased bone formation. Notably, MM tumor growth was suppressed in mice that underwent mechanical loading compared with control mice. We conducted an experiment with mechanical unloading in MM-bearing mice [65]. Right hind legs of mice were immobilized and exposed to mechanical unloading by sciatic denervation or casting with an adhesive bandage. RANKL expression was upregulated in osteocytes that experienced immobilization or mechanical unloading. Mechanical unloading reduced trabecular bone volume, and bone morphometric analyses indicated an increase in osteoclast number and activity. To investigate the effects of mechanical unloading on tumor growth, after sciatic denervation in the right hind legs, we inoculated the same MM cell line with different fluorescein colors, namely green fluorescent protein (GFP) or red fluorescent protein, simultaneously into right and left tibiae, respectively. More MM tumor growth was recorded in the immobilized legs than the intact ones. In addition, extraosseous tumors developed and tumorous lesions outside of the bone were composed of MM cells expressing GFP. In addition, GFP-expressing MM cells were predominantly observed in peripheral blood, indicating that mechanical unloading accelerated MM tumor expansion in bone and egress of cancer cells into the circulation and dissemination outside of the bone (Fig. 4).

Patients with MM often suffer from bone pain and fractures, leading to immobilization or a bed-redden state with mechanical unloading. Mechanical unloading not only induces muscle atrophy but also bone loss with up-regulation of RANKL expression in osteocytes and thereby osteoclastogenesis in the bone marrow (Fig. 4). The increased and activated osteoclasts then enhance MM growth and dissemination in and outside of the bone. These results suggested

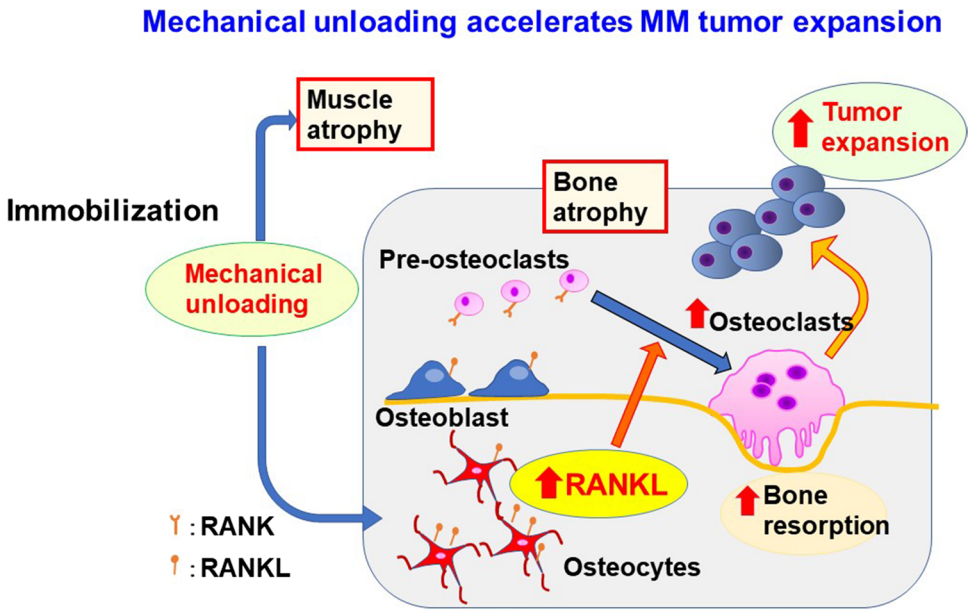

Fig. 4 Mechanical unloading accelerates MM tumor expansion. The mechanical unloading not only induce muscle atrophy but also bone loss with up-regulation of RANKL expression in osteocytes and thereby osteoclastogenesis in the bone marrow. The increased and activated osteoclasts then enhance MM growth and dissemination in and outside of the bone. These results suggest the importance of mechanical loading in maintaining bone mass and suppression of tumor expansion in MM, and also the importance of inhibition of RANKL activity for immobilized patients in a bed-ridden state or paralysis

the importance of mechanical loading for maintaining bone mass and suppression of tumor expansion in MM.

Paradigm shift in MM treatment

Although MM is a heterogeneous disease in terms of MM cell- and patient-related risk factors, major improvements in clinical outcomes of patients with MM in terms of overall survival (OS) has occurred since 2000 owing to the implementation of new agents. Additionally, high-quality responses with minimal residual disease (MRD) negativity can be used as a surrogate of OS and should be achieved [66]. Proteasome inhibitors (PIs) and immunomodulatory drugs are currently the mainstay of MM treatment. However, most patients eventually relapse with drug resistance. To overcome this issue, new combination regimens with therapeutic antibodies have been explored. Adding anti-CD38 monoclonal antibodies, daratumumab or isatuximab, as well as the anti-SLAMF7 antibody elotuzumab offer better results for patients with MM. Furthermore, immune-based therapies, including antibody–drug conjugates, autologous chimeric antigen receptor (CAR) T-cell-based therapies, and bispecific antibodies, have shown promising activity for relapsed disease even with high-risk cytogenetic abnormality.

Elderly patients with poor performance status are often excluded from clinical studies. Establishment of effective treatment for elderly frail patients with MM, for example, those over 90 years old, remains an important issue in the era of longevity.

Treatment for MM bone disease with bone-modifying agents

Bone destruction and renal impairment are common clinical consequences in patients with MM. The MRC Myeloma IX trial, an important study comparing the effect of zoledronic acid intravenous injection every 3–4 weeks and oral daily clodronate from the start of MM treatment for newly diagnosed patients with MM irrespective of image-documented bone lesion(s) [67]. Zoledronic acid effectively suppressed the occurrence of skeletal-related events (SREs) and extended OS by 5.5 months compared with oral clodronate, although the survival benefit was preferentially observed in patients with bone disease at presentation. As such, some guidelines recommend initiating bone therapy with zoledronic acid concurrently with anti-MM therapy in all patients with symptomatic MM (Table 5).

Denosumab is an anti-RANKL neutralizing, fully human monoclonal IgG_2 antibody [68]. Dose adjustments are not required for denosumab administration, because denosumab is not excreted from the kidney, nor metabolized in the liver [69–71]. A single subcutaneous injection of denosumab exerts long-term efficacy [72]. A randomized, double-blind, multicenter phase 3 study of denosumab compared with zoledronic acid in the treatment of bone disease in patients with newly diagnosed MM with at least one image-documented bone lesion [73]. Denosumab met the primary endpoint of non-inferiority to zoledronic acid for the prevention of the occurrence of on-study SREs. Because most on-study SREs occurred within the first 3 months, a post-hoc, landmark superiority analysis of time to first on-study SREs was done at 15 months. Denosumab was more effective in terms of suppression of SRE occurrence. Notably,

Table 1 Patient characteristics

Sex (male/female)	45/39
Median age (range), years	69 (41–88)
Newly diagnosed	61 (73%)
Relapsed/refractory	23 (27%)
Immunoglobulin class	
IgG	49 (58%)
IgA	15 (18%)
IgD	3 (4%)
Light chain only	16 (19%)
Non-secretory	1 (1%)
PS (ECOG)	
0	29 (35%)
1	26 (31%)
2	11 (13%)
3	11 (13%)
4	7 (8%)
Durie and Salmon stage	
I	0 (0%)
II	26 (31%)
III	58 (69%)
A	67 (80%)
B	17 (20%)
ISS stage	
1	26 (31%)
2	31 (37%)
3	27 (32%)
Bone scale	
1	14 (17%)
2	47 (56%)
3	23 (27%)
AL amyloidosis	4 (5%)
Anti-myeloma treatment	
Proteasome inhibitors	84 (100%)
IMiDs	59 (70%)
ASCT	26 (31%)

PS performance status, *ECOG* Eastern Cooperative Oncology Group, *ISS* International Staging System, *SRE* skeletal-related event, *IMiD* immunomodulatory drug, *ASCT* autologous stem cell transplantation

denosumab extended median progression-free survival (PFS) by 10.7 months in an exploratory analysis, although OS was superimposed. The majority (79%) of patients were treated with PI-containing regimens in this study, implying that denosumab may prolong the efficacy of induction treatment with PIs.

We retrospectively analyzed the efficacy of denosumab with PI-based regimens and updated the previously reported data [74]. Patient characteristics are listed in Table 1. All patients were treated with PI-based regimens with denosumab. At the median follow-up of 24 months (interquartile range 1–106), SRE occurred in 8 out of 61 patients with newly diagnosed MM (NDMM) and 6 out of 23 with relapsed/refractory MM (RRMM) (Fig. 5, left). The proportion of patients without SRE at 3 years was 92.3% in the NDMM group and 59.3% in the RRMM group. Factors contributing to the SRE occurrence were MM progression and AL amyloidosis. Bone fractures occurred by falling in 3 out of 4 cases with AL amyloidosis (Fig. 5, right). Balance loss and falling were caused by orthostatic hypotension and muscle weakness at the time of fracture in most cases (Table 2), indicating the importance of retaining physical function to prevent SREs. Bone fractures further deteriorate patients' physical function, and resultant immobilization may accelerate bone loss with the tumor spreading within and outside of the bone.

The characteristics of zoledronic acid and denosumab are listed in Table 3. Zoledronic acid is administered by intravenous drip injection over 15 min or more. Denosumab is given subcutaneously. Zoledronic acid takes 3–4 days to exert its activity, whereas denosumab acts immediately after injection. Zoledronic acid acts on bone-resorbing mature osteoclasts but denosumab can act on immature and mature osteoclasts. Renal toxicity is less with denosumab. The incidence of osteonecrosis of the jaw was similar in both drug arms around 4% per year. Because of its potent activity, patients treated with denosumab have hypocalcemia more often than those treated with zoledronic acid. Risk factors for hypocalcemia in cancer patients after receiving

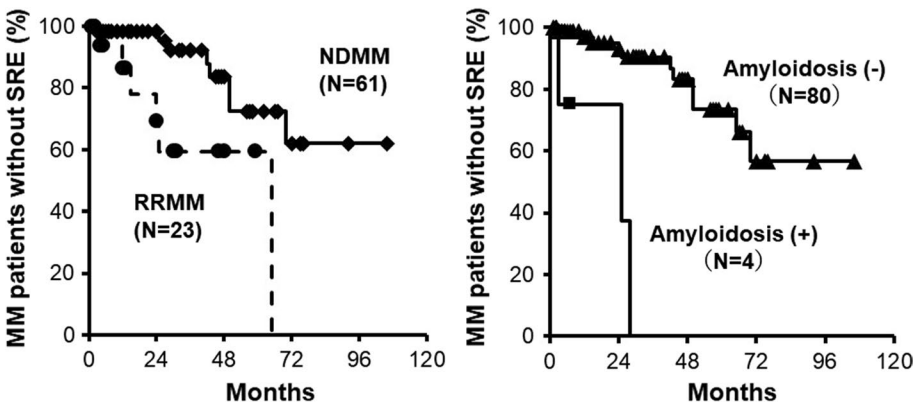

Fig. 5 Proportion of MM patients without SRE. Time to first SRE on denosumab was retrospectively analyzed in 84 MM patients treated with proteasome inhibitor-based regimens between June 2012 and August 2022 in Tokushima University Hospital. The present study was approved by the Institutional Review Board of Tokushima University (permission number 3086-2)

Table 2 Physical function and triggering factors for SRE occurrence

No.	Age/Sex	Amyloidosis	Details of SRE	Treatment response	Triggers	Complications/comorbidities	PS ECOG
1	76/M	None	Femoral fracture	SD	Loss of balance Falling down	Peripheral neuropathy	2
2	47/M	None	Rib fracture Spinal cord compression	PD	None	None	2
3	56/M	None	Pelvic fracture	PD	Loss of balance Falling down	DM type 2 Orthostatic hypotension	4
4	55/M	None	Vertebral fracture Spinal cord compression	PD	None	Peripheral neuropathy	4
5	78/M	None	Sacral fracture Spinal cord compression	PD	None	None	3
6	77/M	None	Vertebral fracture Rib fracture	PD	None	DM type 2 Orthostatic hypotension	1
7	74/F	None	Vertebral fracture	PD	Loss of balance	Peripheral neuropathy	3
8	80/F	None	Vertebral fracture	PD	None	DM type 2 Muscle weakness	3
9	73/F	None	Femoral fracture	SD	Loss of balance Falling down	None	1
10	85/F	None	Vertebral fracture Spinal cord compression	PD	Falling down	None	1
11	59/F	None	Vertebral fracture	PD	None	None	1
12	73/F	Heart, tongue, skin	Femoral fracture	VGPR	Falling down	Muscle weakness Orthostatic hypotension	2
13	78/F	GI tract, skin, muscle	Vertebral fracture	VGPR	Loss of balance Falling down	Muscle weakness	1
14	70/M	Heart, kidney, GI tract	Rib fracture	VGPR	Falling down	DM type 2 Peripheral neuropathy Orthostatic hypotension	0

M male, *F* female, *PS* performance status, *ECOG* Eastern Cooperative Oncology Group, *VGPR* very good partial response, *SD* stable disease, *PD* progressive disease, *GI* gastrointestinal, *DM* diabetes mellitus

Table 3 Characteristics of zoledronic acid and denosumab

	Zoledronic acid	Denosumab
Injection route	iv	sc
Emergence of effects	3–4 days	< 1 day
Target to	Mature OCs	Immature and mature OCs
Hypocalcemia	Sometimes	More often
Renal impairment	+	−
Acute reaction	+	Rare
Bone deposition	+ (cumulative)	−
ONJ	+	+
γδT cell induction	+	−

iv intravenous, *sc* subcutaneous, *OC* osteoclast, *ONJ* osteonecrosis of the jaw

Table 4 Risk factors for hypocalcemia in patients with cancer after receiving denosumab

The first cycle of denosumab treatment
Renal insufficiency
Hypercalcemia before treatment
Aberrantly high baseline serum ALP
Higher baseline bone turnover markers of NTx and BSAP
Potential vitamin D deficiency

ALP alkaline phosphatase, *NTx* N-terminal cross-linking telopeptide of type 1 collagen, *BSAP* bone-specific alkaline phosphatase

denosumab are listed in Table 4. To prevent severe hypocalcemia with denosumab, corrected serum calcium levels should be monitored during treatment, especially in the first cycle of denosumab. Additionally, adequate calcium and vitamin D intake is recommended. Because patients with MM often have renal failure and vitamin D is activated in the kidney, patients with MM with renal failure should take active forms of VD_3 (25-hydroxyvitamin D_3 or 1,25-dihydroxyvitamin D_3) rather than natural vitamin D.

In the guideline issued by the Japanese Society of Hematology [75], it is recommended to administer denosumab or zoledronic acid at the start of treatment in NDMM patients with bone lesion(s). Denosumab is more strongly

Table 5 Guidelines for the treatment and prevention of MM bone disease

	IMWG2021	ESMO2020	NCCN2023 ver.1	ASCO2018
Patient selection	BTAs should be administered to all patients with active MM, regardless of the presence or absence of MM-related bone disease on imaging studies	BTAs should be initiated at MM diagnosis	BTAs should be given in all patients receiving primary MM therapy	BTAs are recommended for patients with active symptomatic MM that requires systemic chemotherapy
Choice of BTAs	Bone disease is present: 1st option, D-mab or ZOL; 2nd option, pamidronate Bone disease is absent: 1st option, ZOL; 2nd option, pamidronate	1st option, D-mab or ZOL; 2nd option, pamidronate	D-mab or ZOL or pamidronate	ZOL or pamidronate; D-mab as an alternative option to ZOL
Dose, and treatment schedule	ZOL 4 mg iv every 3–4 weeks Pamidronate 30 mg (45 min) or 90 mg (120 min) administered every 3–4 weeks	D-mab every 4 weeks ZOL every 4 weeks for 3–6 months, then every 12 weeks	D-mab 120 mg SC every 4 weeks ZOL 4 mg iv every 3–4 weeks Pamidronate 90 mg iv every 3–4 weeks	ZOL 4 mg iv every 3–4 weeks Pamidronate 90 mg iv every 3–4 weeks D-mab 120 mg sc every 4 weeks
Duration	ZOL should be administered monthly for at least 12 months. If patients achieve VGPR or better, physicians can consider decreasing the dosing frequency to every 3–6 months, or ZOL discontinuation	If patients achieve VGPR or better, physicians consider interrupting bone modifying agents after 24 months	Up to 2 years The frequency of dosing (monthly vs. every 3 months) would depend on the individual patient criteria and response to therapy. Continue beyond 2 years based on clinical judgment	Up to 2 years. Less-frequent dosing should be considered in patients with responsive or stable disease
Notes	D-mab might be preferred in patients with renal impairment (Ccr < 30 mL/min)	D-mab is the agent of choice in MM patients with renal impairment (Ccr < 60 mL/min)	D-mab is preferred in patients with renal disease	D-mab may be preferred in patients with impaired renal function

BTA bone targeting agent, *D-mab* denosumab, *ZOL* zoledronic acid, *CR* complete response, *VGPR* very good partial response, *Ccr* creatinine clearance, *iv* intravenous, *sc* subcutaneous injection

recommended in patients with renal impairment due to its low renal toxicity. Current recommendations for the use of bone-modifying agents for patients with MM are listed in Table 5 [76–78]. Most guidelines say that these bone-modifying agents should be given every month for up to 2 years and stopped if the disease is controlled or continued when the disease is active. During the current COVID-19 pandemic, zoledronic acid can be given every 3 months for bone disease prophylaxis. These bone-modifying agents can be discontinued or changed to oral bisphosphonates for patients achieving a good durable response. Oral bisphosphonates may prevent a rebound effect by denosumab discontinuation.

Effects of new anti-MM agents on bone metabolism in patients with MM

MM cells express both constitutive proteasomes and immunoproteasomes. The inhibition of proteasome action results in the accumulation of misfolded proteins and functional proteins to be degraded by proteasomes in the endoplasmic reticulum lumen and cytosol, which facilitates several stresses, including endoplasmic reticulum overload, generation of excess reactive oxygen species, and functional disorder of intracellular proteins, eventually leading to apoptosis. Bortezomib and oral ixazomib are reversible PIs. Carfilzomib irreversibly inhibits both β5 and β5i proteasome subunits at low concentrations to induce more potent and prolonged suppression of proteasome activity in MM cells, compared with the reversible inhibitors bortezomib and ixazomib [79, 80]. Functionally, carfilzomib has been demonstrated to overcome resistance to the first-in-class PI bortezomib [81].

Besides their anti-tumor activity, PIs exerts bone anabolic actions [82–86]. During treatment with PIs, bone formation is restored preferentially in bone-destructive lesions in good responders (Fig. 6) [87]. Patients exhibiting bone formation in bone lesions tend to show a better and prolonged reduction of tumors [88–95]. Therefore, tumor reduction appears to trigger the anabolic effects of bortezomib. PIs induce MM cell death, which reduces the production of anti-anabolic mediators by MM cells and from bone lesions. PIs also suppress DKK1 production by BMSCs and sclerostin mainly by osteocytes [25, 96, 97]. With enough reduction of tumor cells, PIs are able to directly induce critical transcription factor for osteoblastogenesis, including Runx2 and ATF4, and activate osteoblasts to form bone [82, 83, 98, 99].

The REBUILD trial is a notable clinical study with daratumumab monotherapy to evaluate the role of daratumumab in bone remodeling among patients with RRMM [100]. Daratumumab monotherapy did not show statistically significant differences in serum levels of indicators of bone resorption, C-terminal cross-linking telopeptide of type 1 collagen and tartrate resistant acid phosphatase 5b (TRACP-5b), nor changes in the RANKL/OPG ratios over time. In contrast to the weak or marginal suppression of osteoclastic bone resorption, daratumumab showed a positive effect on bone formation with increasing serum levels of bone formation markers, including procollagen type-I N-pro-peptide, bone-specific alkaline phosphatase, and osteocalcin. The anabolic benefit was greater among responders and those with a prolonged duration of treatment. Such anabolic effects were gradually observed even after 4 months in patients on daratumumab monotherapy in contrast to those observed in responders to PIs at early treatment cycles. The anabolic effect of daratumumab was associated with a significant decrease in serum DKK1 and C–C motif ligand-3 levels. Although MM cells substantially influence bone remodeling to skew towards bone resorption, daratumumab can improve bone turnover towards bone formation in responders.

Perspectives

To maintain bone health in patients with MM, controlling MM tumors is required. We can now reduce MM tumors in the majority of patients using induction therapy, but MM

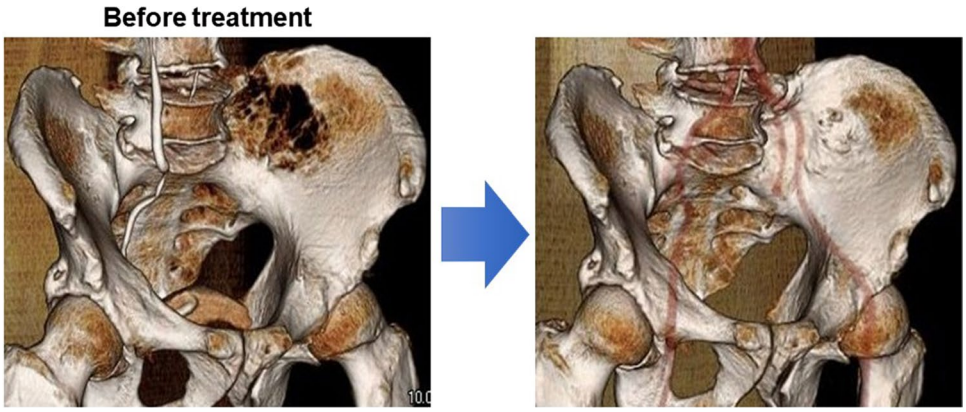

Fig. 6 Bone recovery in responders to bortezomib. A newly diagnosed patient was treated with bortezomib and dexamethasone and achieved a very good partial response after 2 cycles of the treatment. Bone formation appeared in bone defective lesions in the iliac bone (right)

regrows in most cases even after achieving a very good response with MRD negative state. New immunotherapies and/or new drug classes are expected for RRMM, especially for functional high-risk or triple-class refractory MM. To contain MM tumors without a relapse, however, the underlying mechanism of relapse needs to be further clarified. In this regard, we should elucidate the alteration of immune function and the tumor microenvironment in response to different therapeutic modalities. Cytotoxic agents often cause immune dysfunction, which may allow tumor cells to regrow. Additionally, bone marrow microenvironment with increased osteoclasts as well as BMSCs with defective osteoblastic differentiation provide a niche to support MM cell growth and induce tumor drug resistance. Therefore, reshaping of the bone marrow niche-environment and immune system is needed to suppress a relapse.

Risk-stratified therapy should be taken into account with different new agents. To better stratify prognosis, a second revision of the international staging system (R2-ISS) has been recently established [101]. The R2-ISS assigns a prognostic value to each baseline risk feature: ISS stage II (1 point), ISS stage III (1.5 points), del(17p) (1 point), high lactate dehydrogenase (1 point), t(4;14) (1 point), and 1q copy number alterations (0.5 point). Patients are stratified into four risk groups according to the total additive scores: low (0 points), low-intermediate (0.5–1 points), intermediate high (1.5–2.5 points), and high (3–5 points). However, a portion of standard-risk patients has a dismal prognosis, whereas high-risk patients do not always show poor prognosis, indicating that other factors responsible for predicting a relapse should be incorporated into prognostic assessments before treatment and response assessments during or after treatment. Indicators of immune function and bone marrow microenvironment surrounding MM cells may be such factors to be included.

To treat functional high-risk patients, new treatment modalities will play an important role. Among others, immunotherapies, including autologous CAR T-cell-based therapies and bispecific antibodies, are drawing considerable attention. However, we are still quite behind in our understanding of the heterogeneous biology of MM and its implications for therapy. Therefore, we need to further elucidate the efficacy of new agents especially in combinatory treatments with forthcoming treatment modalities such as immunotherapies with CAR T cells and bispecific antibodies to make the best use of these important agents and obtain better and more beneficial therapeutic outcomes in patients with MM.

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Declarations

Conflict of interest M.A. received research funding from Chugai Pharmaceutical, GlaxoSmithKline, Sanofi K.K., Kyowa Kirin, Nippon Shinyaku, Teijin Pharma, and Ono Pharmaceutical, and honoraria from Daiichi Sankyo, Janssen Pharmaceutical K.K., Takeda Pharmaceutical, Sanofi K.K., Bristol-Myers Squibb, and Ono Pharmaceutical. Other authors have no competing financial interests to declare.

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