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Review

Novel Developments in the Treatment of Multiple Myeloma-Associated Bone Disease

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Simple Summary: Multiple myeloma is the second most common hematological malignancy, and the majority of patients have osteolytic lesions by the time of diagnosis. Bone destruction increases the risk of fractures and spinal cord compression, reduces quality of life, and is associated with increased mortality. This paper focuses on current and novel medical and surgical treatment modalities and improvements in prevention and the treatment of therapy-related complications, in particular, medication-related osteonecrosis of the jaw. A special focus reviews new promising targets in the bone marrow microenvironment.



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Abstract: Osteolytic bone disease is present in about 80% of patients with multiple myeloma at the time of diagnosis. Managing bone disease in patients with multiple myeloma is a challenge and requires a multi-faceted treatment approach with medication, surgery, and radiation. The established treatments with intravenous or subcutaneous antiresorptives can cause debilitating adverse events for patients, mainly osteonecrosis of the jaw, which, traditionally, has been difficult to manage. Now, oral surgery is recommended and proven successful in 60–85% of patients. Patients with spinal involvement may benefit from surgery in the form of vertebroplasty and kyphoplasty for pain relief, improved mobility, and reestablished sagittal balance, as well as the restoration of vertebral height. These procedures are considered safe, but the full therapeutic impact needs to be investigated further. Ixazomib, the first oral proteasome inhibitor, increases osteoblast differentiation, and recently published preliminary results in patients treated with Ixazomib maintenance have promisingly shown increased trabecular volume caused by prolonged bone formation activity. Other novel potential treatment strategies are discussed as well.

Keywords: multiple myeloma; kyphoplasty; vertebroplasty; osteonecrosis of the jaw; antiresorptive agents; bone marrow microenvironment

1. Introduction

Multiple myeloma (MM), a plasma cell cancer, is the second most common hematological malignancy [1,2], characterized by the proliferation and expansion of monoclonal

plasma cells in the bone marrow. Osteolytic lesions are a hallmark finding in patients with MM, and as many as 80% of patients have osteolytic bone disease at the time of diagnosis [3]. The increased degradation of bone causes a high risk of skeletal-related events (SRE), such as pathological fractures and spinal cord compression, and greatly contributes to morbidity [4]. The burden of symptoms in patients with MM has a high impact on health-related quality of life (HRQoL), mainly due to reduced physical function and bone pain. Compared to other hematological malignancies, the disease is associated with a higher risk for patients to end up receiving disability pensions [5–7]. Moreover, SRE in patients with MM is associated with inferior overall survival [8]. Thus, managing bone disease in patients with MM is important. In addition to antineoplastic treatment, the treatment of myeloma bone disease may involve radiotherapy, antiresorptives, and percutaneous orthopedic interventions such as vertebroplasty and kyphoplasty, as well as major surgery. The aim of this manuscript is to review the literature and practices of antiresorptive treatments, their adverse effects, and the management of these, along with current standards and new developments in vertebroplasty and kyphoplasty, including examples of bone reconstructive surgery. Antineoplastic treatment and radiotherapy are not within the scope of this review; instead, we focus on potential novel targets in the bone marrow microenvironment.

2. Antiresorptive Treatments

In a healthy individual, bone homeostasis is maintained through the continuous resorption of old bone, which is followed by the coupled refilling (formation) of new bone within the bone resorption cavity. Myeloma bone disease arises in patients with MM due to uncoupled bone remodeling with upregulated osteoclast and downregulated osteoblast activity [9–11]. The receptor activator of nuclear factor- κ B (RANK), a transmembrane receptor expressed in several bone cells as well as in hematopoietic osteoclast precursor cells, activates upon binding with RANK-Ligand (RANKL) and facilitates pre-osteoclast recruitment and osteoclast activation and survival [12]. Myeloma plasma cells increase RANKL expression and decrease osteoprotegerin (OPG) expression. OPG is a decoy receptor that inhibits bone resorption by binding to RANKL and prevents it from binding to its receptor, RANK [13]. The increased RANKL to OPG ratio favors the activation of osteoclasts [14]. The cornerstone in the treatment of MBD is antiresorptive (AR) medication, which inhibits osteoclast activity. Amino-bisphosphonates, zoledronic acid (ZA), and pamidronate (PA), specifically, have for several years been the standard in the treatment of MBD [15]. ZA has the highest relative potency of all bisphosphonates, which is a hundred times higher than that of PA [16]. Either one is recommended as a first choice for all patients with active MM, with or without radiological findings of MBD [17], because micro-architectural changes can be present at the earliest stages of the disease [18]. ZA is preferred, partly because of its more convenient administration time, as well as its superiority over PA regarding mortality rate reduction [19,20]. ZA has shown a progression-free survival (PFS) benefit [21], is not inferior to PA in reducing SREs or bone pain [22], and is superior in treating malignancy-related hypercalcemia [23].

After the discovery of the RANKL pathway, denosumab (Dmab), a human immunoglobulin G2 anti-RANKL antibody, was developed. It inhibits RANKL and is the preferred choice when bisphosphonates are contraindicated (e.g., renal impairment). It is speculated that Dmab could be a viable replacement for bisphosphonates in the treatment of MBD. A large double-blind, double-dummy, randomized trial comparing Dmab to ZA that included 1718 patients, however, found no difference in the median time to the first on-study skeletal-related event and showed no significant difference in incidence for serious adverse events, such as medication-related osteonecrosis of the jaw (MRONJ) [24]. An exploratory end-point was later published from the same study. It found that treatment with Dmab resulted in an increased median PFS by 10.7 months, but only in patients intent on undergoing autologous stem cell transplantation and patients with CrCl > 60 mL/min [25]. Future prospective studies are needed to validate this finding. As of 2021, The International

Myeloma Working Group recommends ZA over Dmab until more data are available [17]. So far, Dmab has been shown to be as effective as ZA in preventing MBD, but it comes at a higher cost. Furthermore, the later discontinuation of Dmab may be more troublesome than the discontinuation of ZA as bone resorption may rebound. This phenomenon will be discussed in detail in a later section. A study is currently investigating if Dmab can effectively delay the time for high-risk smoldering myeloma to transform into MM requiring active treatment ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03792763): NCT03792763, accessed on 1 November 2023), and data are awaited. The recent approval of romosozumab (anti-sclerostin antibody) for the treatment of osteoporotic patients is a promising development that may translate into treatment for patients with MM. It is supported by pre-clinical observations that sclerostin inhibition prevents fractures and pathological bone loss in patients with MM [26–28].

3. Medication-Related Osteonecrosis of the Jaw and Multiple Myeloma

The jaws are rarely symptomatically affected directly by the cancer as much as the spine and hip bones. However, the high-dose AR treatment involves a risk of developing MRONJ. One nationwide population-based cohort study in Denmark found the incidence of MRONJ to be around 2% in patients treated with high-dose AR [29]. Other studies have found ZA MRONJ incidence to be from 2.6% to 4% [20,30]. Importantly, however, is that the incidence of MRONJ rises with higher cumulative doses of, or treatment duration with, AR therapy [31]. One systematic review and meta-analysis including a total of 42,003 patients with different malignancies showed that with 4 mg of ZA every 3 or 4 weeks, MRONJ incidence was 2.0% versus 1% when ZA was given every third month. MRONJ incidence with 120 mg Dmab given every month was 2.09%, whereas it was zero when 60 mg was given every 6 months [32]. However, in the currently recommended treatment regimes in MM, 120 mg Dmab or 4 mg ZA both given every four weeks, a large randomized phase 3 study including only MM patients found the risk of developing MRONJ to be similar between the two treatments [24].

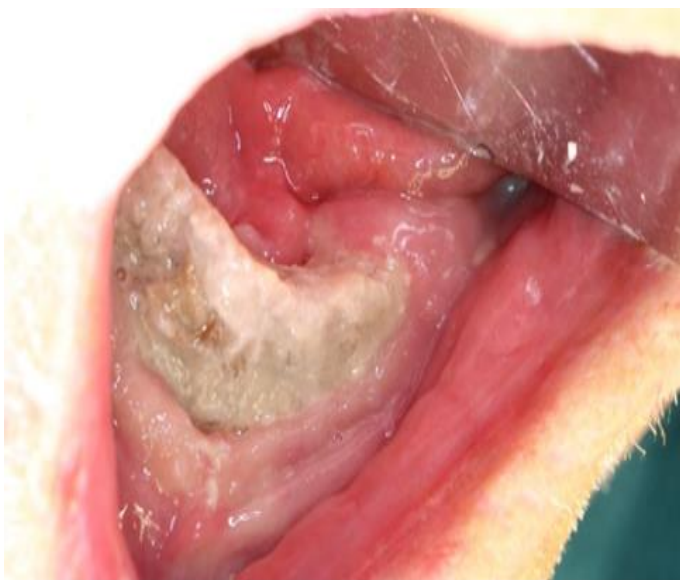
The precise mechanism behind MRONJ development is not fully understood, but the development is closely associated with dental extraction or pressure damage from oral prostheses [33]. Theories involve micro-trauma or infection in the bone, triggering an impaired bone healing process, which leads to inflammation with compromised blood supply and subsequent bone necrosis. Recent studies indicate that infection probably is the major determinant of MRONJ [34–37] and, thus, eliminating local infection may prevent the development of MRONJ. Dental extraction and minor oral surgeries can safely be performed with minimal risk of MRONJ when performed in combination with prophylactic antibiotic therapy [38–40]. Additional risk factors include smoking and diabetes as these also compromise healing and increase susceptibility to oral infections after treatment. Prevention and risk reduction of developing MRONJ include appropriate dental treatment before initiating antiresorptive therapy, close monitoring during treatment, and regular dental evaluations to prevent developing dental infections following AR initiation [41].

Temporary discontinuation of AR treatment before upcoming oral surgery, known as a drug holiday, has been considered as a strategy to minimize the risk of MRONJ. However, a large meta-analysis including a total of 6808 patients found no significant difference in the development of MRONJ between the drug holiday group ($n = 4847$) and the control group ($n = 1961$) [42]. One RCT included 23 patients undergoing surgical tooth extraction and randomly allocated patients to a drug holiday from 1 month prior to 3 months post-surgery, with the majority of patients receiving Dmab. It also found no evidence of drug holidays preventing MRONJ. They did, however, report a decline in the patient-reported health state in those on a drug holiday compared to those in the drug-continuation arm [43].

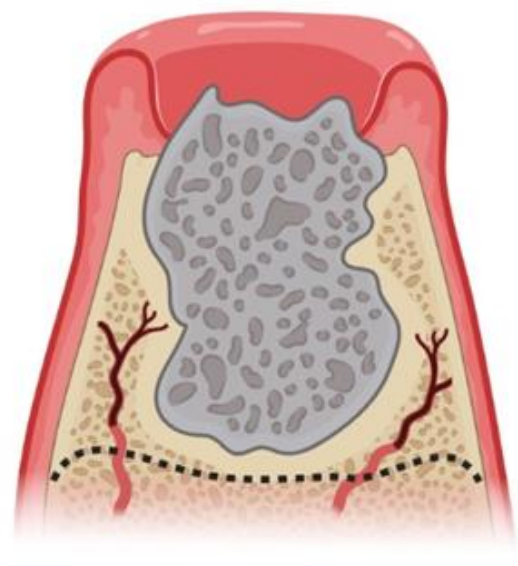
Diagnosing MRONJ is based on radiological and clinical findings, including exposed necrotic bone and fistulas to underlying necrotic bone, with symptoms such as jaw pain, non-healing ulcers, and soft tissue swelling. Radiological imaging can help distinguish MRONJ from other oral pathologies and help stage the amount of necrosis for subsequent treatment planning. Conservative treatment was previously recommended for patients

with MM who developed MRONJ [44] as this was believed to slow or stop the progression of osteonecrosis. This may include antibiotic therapy, local oral hygiene maintenance with chlorhexidine, the removal of sequestered bone, or minor debridement of the site [44]. However, a recent study shows that despite conservative treatment, MRONJ still progresses in 80% of patients with stage I MRONJ [45]. Thus, the European task force on MRONJ now recommends surgical treatment, when possible, but conservative treatment may still be indicated in frail, elderly patients or in a palliative setting [33].

Recommended surgical treatment (Figure 1) consists of resection of the osteonecrotic tissue and primary closure of the gingiva. The procedure is planned from a 3D cone beam or multislice CT scan. Surgical treatment is performed in combination with antibiotic therapy (amoxicillin with clavulanic acid, 3 g/day, a minimum of one day before and 6–9 days after surgery) [46]. An incision is made that extends from the perforation of the osteonecrosis in both mesial and distal directions on the alveolar ridge. The gingiva is carefully elevated to access the osteonecrotic tissue and the bone is resected with a drill to the planned extension and depth. The remaining bone should display vital bleeding points. Biopsies can be taken from the vital bone and from the resected necrotic bone to confirm the diagnosis of MRONJ, eliminate an additional cancer diagnosis, and confirm vital bone in the margins of the resection. Finally, the gingiva is mobilized and sutured to a tension-free primary closure. In case the gingiva cannot close the defect, a cutaneous flap must be raised to close it. Surgical treatment has been shown to successfully remove necrosis and infection in more than 60 to 85% of treatments [47]. To increase the chance of successful surgical treatment, adjuncts to surgery, such as teriparatide [48,49] platelet-rich fibrin/plasma [50], and growth factors [51], have shown promising results, but require further investigation. Additionally, fluorescence-guided surgery also shows an increase in success rates by ensuring that all the infected and necrotic bone is removed [52,53]. Overall, the level of evidence for optimal treatment is low for all treatment protocols, building on few randomized controlled trials [37]. The preferable and most effective measure seems to be the prevention of MRONJ by preventing infection and inflammation in the bone by dental examination at 3-month intervals [39].

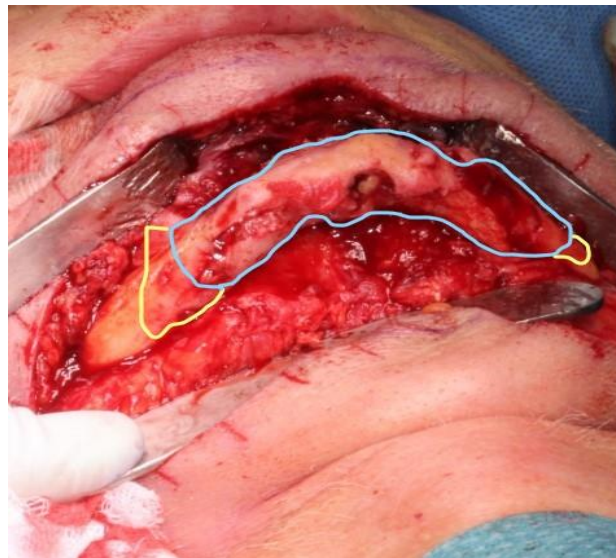


(A)



(B)

Figure 1. Cont.



(C)

Figure 1. (A) Clinical presentation of medication-related osteonecrosis of the jaw (MRONJ). The stage 3 osteonecrosis in the anterior part of the mandible is clinically visible as grey bone protruding through the inflamed gingiva. (B) MRONJ. The figure shows the area of necrosis and the suggested resection area for resection. The edges are slightly rounded to avoid sharp edges that may perforate the gingiva during healing. (C) Surgical treatment with submandibular incision to access the necrotic bone. A wide incision is necessary to ensure that all necrotic bone is removed, and the mandible can subsequently be restored by a reconstruction plate. Blue line marks the extension of visible osteonecrosis. Yellow line marks the intermediate, sclerotic zone.

4. Antiresorptive Agents and Duration of Treatment

Before the emergence of MRONJ, AR treatment usually continued indefinitely. However, since incidences of both MRONJ and atypical femur fractures [54,55] increase with the dose and duration of AR treatment, guidelines have been updated to reflect this and reduce its usage. Since the original studies with ZA and PA had a follow-up of approximately 2 years, this is what most guidelines recommend [19,56]. The British Myeloma IX study, however, found that the increased protective effect of ZA compared to the inferior clodronate remained significant beyond 2 years of treatment. Likewise, a Mexican study found a 20% reduction in SRE in patients with MM receiving ZA for 4 years compared to only 2 years [57]. A recent presentation at IMW 2023 presented data from the Magnolia trial, a randomized study comparing 2 vs. 4 years of treatment with ZA in patients with MM, found that the risk of progressive bone disease (PBD) was significantly lower in the 4-year ZOL arm, with a hazard ratio of 0.38, without an increased significant risk of MRONJ [58]. To mitigate the risk of side effects with prolonged AR treatment, some guidelines suggest that the treating physician can consider decreasing the dosing frequency after 12 months of treatment to every 3 months for patients obtaining VGPR or better [15]. This is mainly based on the Myeloma IX study, which found that the positive effect of ZA over clodronate on PBD disappeared in patients that had obtained CR + 100 days after autologous stem cell transplantation [59]. However, clinical studies have also demonstrated that patients obtaining a deep response post-transplant have a very low risk of future PBD [60]. Two studies including mainly patients with other malignant diseases than MM found treatment with ZA every 12 weeks versus every 4 weeks to be non-inferior; in these studies, the 12-week schedule was initiated at diagnosis [61,62]. Whether or not these data justify the de-escalation of AR based on response depth still has not been tested prospectively. We know from the Magnolia trial that 24% of all cases of PBD were indeed observed in patients who had obtained CR in their latest line of treatment [63]. Furthermore, it has been demonstrated that stopping ZA after 12 months of treatment results in a shorter suppres-

sion of bone resorption, reflected by lower levels of bone resorption markers, compared to 24 months of treatment [64]. It thus seems that 48 months of treatment with AR is superior to only 24 months of treatment. Whether dosing can be reduced to every 12 weeks, or if patients with a certain depth of response may tolerate less treatment, remains to be tested prospectively. A future alternative approach to determine which patients can safely descale or pause AR treatment could perhaps be taking measurements of circulating microRNA. MicroRNAs have recently been shown to play an important role in osteoblasto- as well as osteoclastogenesis [65]. In addition, the same microRNAs are able to accurately predict the presence of osteolytic bone disease in newly diagnosed multiple myeloma [66].

Importantly, however, discontinuation of ZA and Dmab have very different effects on bone remodeling. Discontinuation of ZA results in a gradual declining effect, while discontinuation of Dmab may result in a devastating resorptive rebound phenomenon, probably due to an underlying upregulation of RANKL. Studies including patients with other diseases than MM have shown that terminating treatment with Dmab, or even a brief temporary discontinuation, may result in severe bone resorptive rebound, leading to an increased risk of multiple vertebral fractures [67–70]. A direct transition from Dmab to ZA has shown to diminish, but not prevent, this rebound phenomenon [71], and this approach may not be viable in patients on Dmab with reduced renal function. A practical approach in these patients could be to not discontinue treatment with Dmab but only reduce the intensity to every 12 weeks. Another proposed way to counter this problem is a combined short-term regimen with teriparatide and Dmab [72]. The Federal Drug Administration (FDA), however, has placed a black box warning on teriparatide for patients with skeletal malignancies as it increases the risk of osteosarcoma in rats.

If AR treatment is completely discontinued, we know from the Azabache trial that it should be re-initiated at biochemical progression [73].

5. Vertebroplasty and Kyphoplasty

Vertebral compression fractures are a common complication of myeloma bone disease, resulting in severe pain and functional impairment. Surgical interventions, such as vertebroplasty and kyphoplasty, have emerged as effective treatment options for pain relief and the restoration of vertebral height in these patients [74,75]. Vertebral augmentation, vertebroplasty, and kyphoplasty are minimally invasive procedures performed under fluoroscopic guidance. Vertebroplasty involves the percutaneous injection of polymethylmethacrylate (PMMA) into the fractured vertebral body, providing stabilization. Kyphoplasty includes an additional step of balloon inflation to restore vertebral height before PMMA injection. These procedures are typically performed on an outpatient basis under local anesthesia with light sedation. The indications for vertebroplasty and kyphoplasty in patients with MM with vertebral compression fractures include symptomatic fractures and severe pain that is unresponsive to conservative management [75]. The protection of sagittal balance has emerged as an important indication, with increasing long-term survival rates in the MM population [75].

Several studies have reported favorable clinical outcomes following vertebral augmentation procedures in patients with MM [74,76,77]. Significant pain relief, improved mobility, and the restoration of vertebral height have been observed [74,76,78]. These interventions have shown a reduction in pain scores, decreased analgesic requirements, and improvements in quality of life [74,76,78]. Moreover, they are associated with low complication rates and minimal perioperative morbidity [74,79–81]. A Danish national clinical guideline for the treatment of malignant lesions with percutaneous vertebroplasty, published in 2020, includes a weak recommendation for the procedure [82]. However, the number of high-quality studies to uncover the full impact of the procedures is still low. Presently, a single-blinded, randomized clinical trial is being conducted to compare the outcomes of standard care alone versus standard care supplemented with vertebroplasty (clinicaltrials.gov: NCT04533217, accessed on 1 November 2023) [83]. Wedge osteotomy can be considered in cases where severe kyphotic deformity affects the patient's activi-

ties of daily living. It allows for the reestablishment of sagittal balance and correction of deformity (Figure 2).



Figure 2. Lateral standing X-ray images before (**left**) and after (**right**) wedge osteotomy in a patient with MM with multiple vertebral lesions treated with vertebroplasty. Note the correction of the sagittal profile.

6. Targeting the Microenvironment

Myeloma bone disease is characterized by the development of focal “punch-out” lesions, which are the result of a highly active bone resorption with an uncoupling of the subsequent bone formation. The uncoupled bone formation is likely a consequence of myeloma cell-induced disruption of the bone remodeling compartment (BRC) canopies (Figure 3), which reflect a bone marrow envelope that is lifted above remodeling sites [84]. The canopies/envelope consist of elongated osteoprogenitor cells that physically separate the bone surface cells, including remodeling events from the bone marrow cavity [10,85], considered to be a local reservoir of osteoprogenitor cells [84,86]. This local reservoir is critical for the transition from bone erosion to formation, requiring the recruitment of a critical density of osteoprogenitor cells to the eroded surfaces formed by bone-resorbing osteoclasts. It has previously been shown that the number of osteolytic lesions in patients

with MM is directly correlated to the uncoupling of bone resorption and bone formation and that this uncoupling occurs primarily upon MM disruption of the canopies [10]. The mechanisms of canopy disruption are not fully understood, but it may be mediated by cancer-induced apoptosis of the canopy cells [11], as myeloma cells have been shown to induce apoptosis in osteoblastic cells via tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and Fas-Ligand (FasL) [87,88].

Upon gaining proximity to the bone surface cells, the MM cells upregulate osteoclast activity and differentiation along with osteoblast hypoactivity, altering the tightly coupled process of bone remodeling. The bidirectional effect of myeloma on bone cells is mediated by a myriad of osteoclast-activating factors, such as RANKL, macrophage inflammatory protein alpha (MIP-1 alpha), interleukin-1 (IL-1), interleukin-3 (IL-3), and tumor necrosis factor alpha (TNF- α) [89–91], and osteoblast-inhibiting factors like dickkopf WNT signaling pathway inhibitor 1 (DKK1), sclerostin, hepatocyte growth factor (HGF), interleukin-7 (IL-7), and TNF- α [92–96]. MM cells additionally express syndecan-1, which binds OPG, resulting in its endocytosis and degradation, further contributing to osteoclastogenesis [97]. In addition to the autocrine effect of myeloma cells on osteoclasts and osteoblasts, their modulation of the proximal bone marrow microenvironment also results in the further release of RANKL, macrophage colony-stimulating factor (MCSF), interleukin-6 (IL6), and TNF- α from bone marrow stromal cells [98–100] or osteoblast inhibitory factors like sclerostin from osteocytes [26,28,101–103], among others. Increased bone resorption leads to the release of growth factors from the bone matrix, which, in turn, promote cancer cell growth, leading to a reciprocal interaction known as the “vicious cycle”.

In addition to their direct and indirect effects on bone cells, myeloma cells modify other bone marrow microenvironment components that consequently support their engraftment, growth, and survival. Co-culture experiments demonstrate that MM cells inhibit adipocyte differentiation, promote adipocyte lipolysis, and uptake fatty acids from proximal adipocytes [104,105]. In turn, myeloma-modified adipocytes support cancer growth and survival, demonstrating a shift towards a pro-tumorigenic microenvironment upon cancer cell colonization.

Skeletal stem and progenitor cells (SSPCs, known as mesenchymal stem cells) also play a crucial role in MBD and are distinctly altered by the presence of MM cells in both a paracrine and an autocrine fashion. SSPCs reversely alter MM cell phenotype and function by the secretion of micro-vesicles and cytokines that stimulate MM cell proliferation and migration [106–108], contributing to the establishment of a pro-tumorigenic microenvironment. In turn, SSPCs differentiation capacity is hampered in MM [109–111], resulting in osteoblastopenia [112] and an accumulation of SSPCs in the bone marrow [113]. Furthermore, SSPC gene expression is largely altered by MM, as demonstrated by in vitro co-culture studies of SSPCs with MM cell lines [114,115]. Even after ex vivo expansion of SSPCs without MM cells, the gene expression profiles of SSPCs from patients with MM are distinguishable from SSPCs from patients with premalignant monoclonal gammopathy of undetermined significance (MGUS; an asymptomatic condition that precedes MM) and healthy donors [114,116–119]. Deregulated transcriptional pathways include cell cycle regulation, osteoblast maturation, MM cell survival factors, and immune-modulating factors [117,119]. The deregulation of gene expression in SSPCs persists after anti-myeloma therapy [113,118,119], even in patients who are negative for measurable residual disease [119], suggesting a permanent modulation of the cells. This is supported by findings of genomic alterations [120] and epigenetic modifications of the SSPC genomes in MM, dependent on disease stage and inducible by MM cell co-culture [121]. While recent years’ advances in anti-myeloma therapy have improved survival in patients with MM tremendously [122], there has been no revolution in the treatment of myeloma bone disease, which still relies mainly on AR therapies.

Novel treatments targeting alterations of SSPCs could suppress the pro-tumorigenic bone marrow microenvironment while stimulating the differentiation of osteoblasts with bone-forming capacity and even anti-myeloma effects [123,124]. Proteasome inhibitors

have been shown to exert some of their therapeutic effects, not only by their anti-tumor effect on myeloma cells but also through the off-target inhibition of the nuclear factor- κ B (NF- κ B) signaling pathway, which results in decreased RANKL-mediated osteoclastic differentiation [125]. Indeed, Bortezomib increases serum bone formation markers and decreases markers of bone resorption in clinical studies [126,127]. Another proteasome inhibitor, carfilzomib has been shown to promote increased trabecular bone volume in a mouse model of MM [128]. Furthermore, in a clinical trial with humans, carfilzomib has been shown to increase the bone formation markers osteocalcin and procollagen type I N-propeptide, independently of myeloma response to treatment [129].

The proteasome inhibitors' improvement of the skeletal compartment is, however, overshadowed by problematic adverse toxicities, such as neuropathy and cardiac toxicity [130–132], and by the development of resistance in MM cells. Ixazomib, the first oral proteasome inhibitor, has proven to be more tolerable in clinical trials. In addition to its anti-tumor effect [133], it also improves osteoblast differentiation while inhibiting osteoclast differentiation in in vitro studies [134,135]. The effect of ixazomib on myeloma bone disease is currently being investigated in a clinical trial on patients with MM in remission ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04028115) NCT04028115, accessed on 1 November 2023). Recently published preliminary results from this trial [136] revealed a drug-mediated increase in trabecular bone volume mediated by decreased osteoclast activity and longer bone formation events in bone biopsies taken after just 3 months of treatment [136]. Daratumumab, a CD38 antibody that is extensively used to treat MM, has also demonstrated positive effects on bone formation. Whether this is due to a direct effect on the osteoblasts or through an indirect effect on the myeloma cells needs further exploration [137]. A quick overview of possible bone-targeting therapies can be obtained from Table 1.

Table 1. Major or novel bone targeting therapies and their mechanism of action.

Drug	Target	Pathway	Mechanism of Action	Reference
Zoledronic Acid (bisphosphonate)	Osteoclasts	Mevalonate pathway	Inhibits bone resorption	[138]
Denosumab (monoclonal antibody)	RANK	RANK/RANKL pathway	Inhibits bone resorption	[12]
Daratumumab (monoclonal antibody)	CD38	Antibody-dependent cellular cytotoxicity (ADCC) Complement-dependent cytotoxicity (CDC) Direct apoptosis	Signaling events, receptor-mediated adhesion, regulation of migration	[139]
Romosozumab (monoclonal antibody)	Sclerostin	Wnt-signaling pathway	Inhibits osteoclastogenesis and perhaps stimulates bone formation	[140]
Ixazomib (proteasome inhibitor)	20S proteasome (proteasome subunit beta type-5)	Ubiquitin-proteasome pathway	Inhibition of NF- κ B signaling Cell cycle arrest Cell apoptosis Stimulates osteoblast differentiation Inhibits osteoclast differentiation	[141]

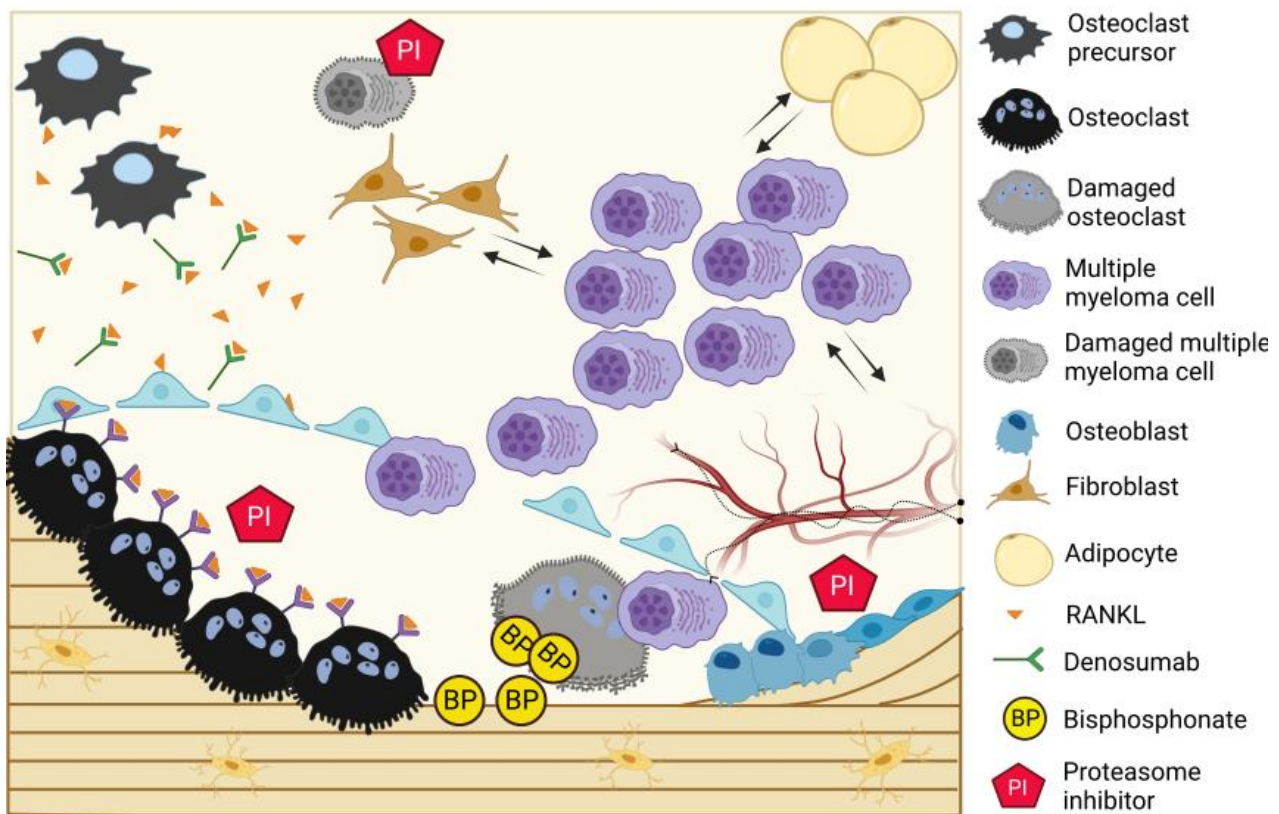


Figure 3. Current therapies in myeloma bone disease. MM cells interact with their surrounding bone marrow microenvironment, including vasculature/innervation, SSPCs, and adipocytes, which, in turn, promote MM cell survival and proliferation. Upon disruption of the bone remodeling compartment (BRC) canopy, MM cells enter into direct contact with osteoclasts, osteoblasts, and osteoprogenitor cells, uncoupling the bone resorption and formation and inducing osteolytic disease. Bisphosphonates bind the bone surface and promote osteoclast apoptosis and Dmab binds RANKL, thereby decreasing osteoclast differentiation. Ixazomib, a proteasome inhibitor, decreases osteoclast activity and simultaneously promotes longer bone formation events by osteoblasts, resulting in net bone gain.

Importantly, the sum of the described MM-induced alterations to the bone marrow microenvironment drives the production of anti-apoptotic cytokines and suppresses anti-tumor responses, resulting in an environment supporting MM cells' growth, survival, and resistance to therapy—termed “the MM niche”. This niche plays a pivotal role in the induction of MM dormancy [142,143], a state of quiescent growth arrest that allows MM cells to become unavailable to anti-myeloma therapy. Here, osteoblastic cells may control dormancy induction, while osteoclastic bone remodeling may promote dormancy escape and consequent disease relapse [144]. These residual MM cells accumulate mutations over time, driving later disease relapses and resulting in the incurable disease that is MM; thus, targeting myeloma bone disease may ultimately pose an effective avenue towards disease cure.

7. Conclusions and Future Perspectives

Myeloma bone disease remains a challenging condition to manage. Vertebral compression fractures are painful and immobilizing and thereby are potentially dangerous. Surgical interventions with a focus on pain relief and restoring the sagittal balance indicate a very low perioperative risk versus a great therapeutic value, but the full therapeutic impact still needs to be investigated further. AR treatment is necessary for patients with MM, but, for a small number, it can bring debilitating adverse events, such as MRONJ, that is difficult to

manage. AR therapy regimes could benefit from prolonging treatment periods from two to four years in order to reduce the risk of PDB. But, since the incidence of MRONJ rises with the cumulative dosage of antiresorptive medication, the treating physician might consider reducing the dosing frequency to every 3rd month for patients who achieve VGPR or better after their anti-myeloma therapy.

In the treatment of MRONJ, conservative treatment was previously the preferred option, but, now, surgery is recommended and is successful in 60–85% of patients. Overall, the treatment protocols lack high-grade evidence, and several adjuvating therapies are being investigated. No consensus has been reached on drug holidays and whether these are beneficial in preventing MRONJ, and the preferable and most effective measure seems to be the prevention of MRONJ by preventing infection and inflammation in the bone by regular dental examinations.

A major breakthrough in myeloma bone disease treatment is still awaited, and research should continue to investigate bone anabolic treatments. Romosozumab, the anti-sclerostin antibody approved in treatments for osteoporosis, could be relevant in the treatment of myeloma bone disease. Further, proteasome inhibitors stimulating the stromal cells in the bone marrow microenvironment show promise in inducing bone healing and also potentially diminishing the risk of myeloma progression. Ixazomib, the first oral proteasome inhibitor, is currently being investigated in this respect, and preliminary data are promising.

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