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Scientific Research

Biology and Treatment of Skeletal Manifestations in Multiple Myeloma

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Abstract

MM is frequently associated with the development of osteolytic bone lesions, osteoporosis and pathological fractures. Bone destruction in MM is caused by osteoclasts recruited in areas adjacent to myeloma plasma cells; their contact triggers both cell types to secrete soluble factors sustaining one each other's activation and proliferation. Osteoclasts differentiate and maturate upon binding of the receptor activator of NF-kappaB ligand (RANKL), secreted by bone marrow microenvironmental cells, to its receptor (RANK) on osteoclast progenitors, while osteoprotegerin (OPG), a natural decoy receptor, can block the aforementioned ligation. At the same time osteoblasts are inactivated by the Wnt/β-catenin signaling pathway inhibitor, Dickkopf-1 protein (DKK-1), secreted by malignant plasma cells. Furthermore, DKK-1 deregulates the OPG/RANKL equilibrium, promoting osteoclastogenesis. Myeloma bone disease (MBD) can be treated with myeloma-directed chemotherapy and agents inhibiting bone resorption such as aminobisphosphonates, although new promising biology driven monoclonal antibodies targeting osteoclastogenesis mechanisms are emerging. Palliative MBD treatment includes analgesics, orthotics, radiation therapy, vertebroplasty and kyphoplasty. In case of spinal cord compression, radiation therapy or surgical decompression, should be instantly performed, along with steroid administration. Surgery may also be an option especially in case of weight-bearing bone fractures. MBD is a morbid complication and should be carefully managed because it deteriorates patients' quality of life and worsens dis-

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ease outcome.

Keywords

Multiple Myeloma, Skeletal Manifestations, Biology, Treatment

1. Introduction

Multiple myeloma (MM) is a relatively frequent hematological neoplasm that is characterized by bone marrow (BM) infiltration by malignant plasma cells secreting a monoclonal component in the serum or urine. Disease symptomatology includes a wide range of manifestations among whose skeletal ones are the most frequent concerning about 80% of newly diagnosed symptomatic patients [1]. Therefore, bony signs are included in the CRAB criteria for the recognition of symptomatic patients in need of immediate treatment. The aforementioned criteria comprise hypercalcemia (C), renal complications (R), anemia (A) and bone disease (B) [2]. Patients' median survival is of about 4 - 5 years with increasing evidence of outcome improvement with the systematic use of new drugs [3]. Significant morbidity may be observed during disease course, partly due to bone pains although considerable progresses have been made in skeletal supportive care.

Bone disease underlying pathophysiology is intrinsically related to MM biology itself and the better understanding of both has leaded to new potent therapeutic modalities.

In the present context, our purpose is to describe the biologic background and the therapeutic state of the art in relation with MM skeletal manifestations and to present, in addition, some relevant results from our group.

1.1. Myeloma Related Skeletal Manifestations

Approximately 60% of symptomatic MM patients suffer from bone pains [4]. Although clinical manifestations of MM are variable, spontaneous fractures, osteoporosis and spinal cord roots compression symptoms are additional clinical findings at diagnosis and throughout disease course that lead to increased morbidity [1] [5]. Lytic lesions, related to osteoclast activation induced by a network of cytokines, are a hallmark of MM [6]. The development of bone destruction is a catastrophic complication for most patients with malignancies and among cancers or hematologic malignancies, MM is the first cause of bone involvement; likewise, Saad *et al*. evaluated over a 21 months period a series of 3049 patients suffering from malignancy-related bone disease, and showed that the highest incidence of spontaneous fracture (43%) was observed in MM patients, as compared to breast, prostate and lung cancer [7].

Bone destruction in MM can involve any bone [6], most likely the spine (49%), skull (35%), pelvis (34%), ribs (33%), humerus (22%) and femur (13%) as shown in **Figure 1**. The pelvis and proximal femur are common sites of solitary plasmatocytoma [5].

Bone plasmacytomas are plasma cell masses arising from bones; they may affect the blood supply of the spinal cord, the vertebras' columns, the meninges or the nerve roots, thus leading to sensation defect, muscle weakness and dysfunction or even loss of bladder of bowel sphincter control. These emergency issues require immediate management in order to avoid paralysis [6] [8].

According to guidelines, myeloma bone disease (MBD) is assessed by skeletal x-rays of the skull, chest, spine, pelvis, humeri, and femora, although conventional radiographic findings are not sensitive enough to reveal small lesions and efforts are made to improve MBD routine imagine. Nevertheless, about 80% of MM patients present at diagnosis, some kind of MBD, as assessed by x-rays, including diffuse osteoporosis, multiple lytic lesions and 25% spontaneous fractures. Death risk is increased by more than 20% in MM patients with fractures. Moreover Durie and Salmon included conventional radiographs' findings in their staging; they built a bone scale and patients were scored 0 when no lesions were seen, 1 in the presence of diffuse osteoporosis and up to 1 osteolysis, 2 with multiple osteolyses and 3 when extensive lytic changes with pathologic fractures were observed. Scale 4 patients were automatically staged III [9].

In a study on 260 MM patients, with a median survival of 38 months, skeletal lytic changes strongly correlated with time to treatment but showed only a trend for decreased survival in patients with Durie and Salmon bone scale 3 - 4 [10]. We examined the same in a series of 177 consecutive MM patients and found that those

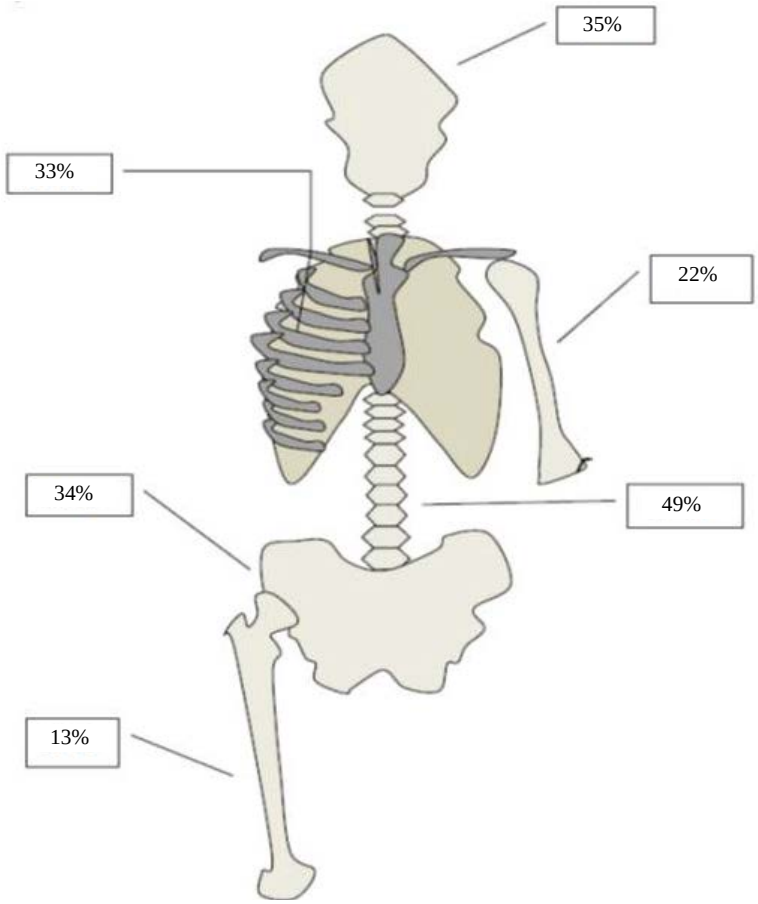

Figure 1. Skeletal distribution of multiple myeloma.

suffering from spontaneous fractures at diagnosis, representing the 24%, faced a worse outcome with an median overall survival of 30 months compared to 86 months ($p < 0.00001$) (**Figure 2**).

1.2. Underlying Biology

In the bone marrow of MM patients, a continuous interplay between malignant plasma cells and microenvironmental cells, lead to cytokine production, mediators' expression and signaling pathways activation, thus contributing to plasma cells proliferation, expansion and disease evolution. An important process that takes place within the medullar environment includes the interactions between plasma cells and osteoclasts (OC). Osteoclasts are the primary bone-resorbing cells in both normal and neoplastic states. Bone destruction in MM is caused by OC proliferating in bony areas adjacent to myeloma cells. Both MM and OC cells secrete soluble factors that sustain each other's activity [11] [12]. Cytokines involved in osteoblasts and osteoclasts regulation are presented in **Table 1**, while their main biological actions and clinical consequences are described below.

1.2.1. OPG/RANKL

Proliferation, differentiation and apoptosis of OC are normally regulated by members of the tumor necrosis factor family of receptors and ligands [13]. The receptor of NF-kB ligand (RANKL) expressed on the surface of BM stromal cells, binds to its receptor RANK expressed on OC precursors, leading to osteoclast formation and activation [14] [15]. This process can be inhibited by osteoprotegerin (OPG), a soluble decoy receptor, that interferes between RANK and RANKL bounding, thus inhibiting OC development [12] [15] [16]. The expression of RANKL and OPG is normally controlled by hormones, growth factors and cytokines [17]. In MM, malignant cells themselves were found to express RANKL and furthermore to trigger RANKL expression by other cells; furthermore, myeloma cells were shown to decrease OPG concentrations in the local environment, possibly by

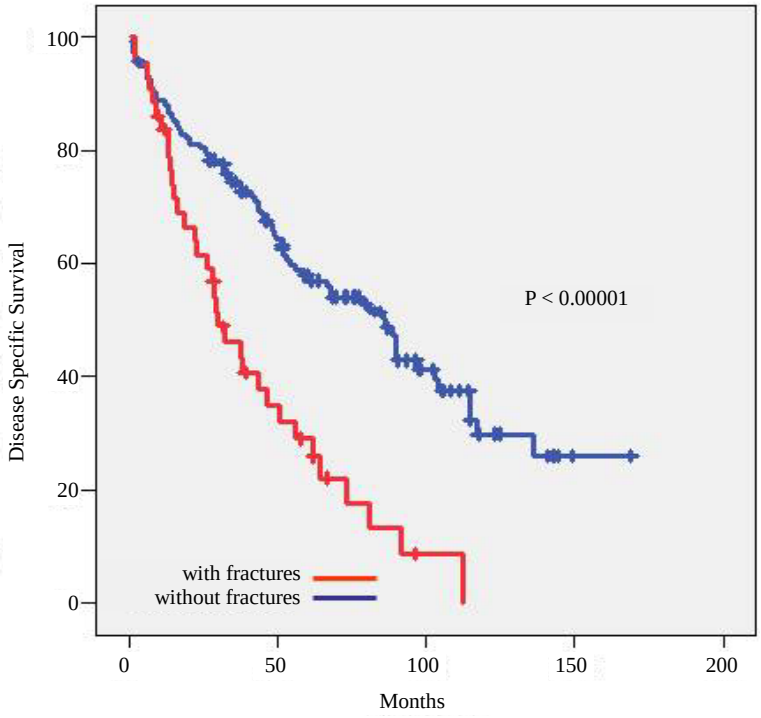

Figure 2. Disease specific survival. Life expectancy in patients with and without fracture.

Table 1. Cytokines involved in osteoblasts and osteoblasts regulation.

Cytokine	Osteoblasts		Osteoclasts	
	Upregulation	Downregulation	Upregulation	Downregulation
RANKL				√
OPG	√			
TGF-b				√
PDGF				√
IGF I, II				√
BMPs	√			√
TNF-a			√	
IL-1			√	
IL-3		√		
IL-6			√	
MIP-1a			√	
DKK-1		√		
VEGF			√	
b FGF			√	

its internalization and degradation [18]. In addition, some groups reported that serum OPG levels in MM patients were inversely associated with bone disease and were decreased as compared to normal individuals [19];

on the contrary serum soluble RANKL was found elevated in MM, while the soluble RANKL/OPG ratio was increased and correlated with bone disease and overall survival [20]. Other groups however, including ours, found higher serum OPG levels in MM patients as compared to healthy individual [20]-[29] while in addition, serum OPG correlated with adverse prognostic markers such as increased beta2-microglobulin. Published diverging results on serum OPG levels are shown in **Table 2**. Recombinant OPG is effective in suppressing bone resorption in postmenopausal women [30], but the initial enthusiasm to administrate it in patients with MM [31] was abandoned and scientific community interest turned toward monoclonal antibodies against RANKL. Denosumab is a human monoclonal IgG_2 antibody that selectively binds to RANKL and is currently tested in MM patients for the prevention of bone destruction; results are encouraging and it was shown to produce a more rapid decline in bone turnover markers within 12 hours of injection compared to aminobisphosphonates, that are for the time being the standard of care for MBD [32].

1.2.2. Dickkopf-1

Dkk-1 (Dickkopf-1) protein is a natural inhibitor of Wnt/β-catenin signaling pathway that is responsible for the differentiation of osteoblast precursors. Bone cells homeostasis is regulated by Wnts, a family of 19 glycoproteins that up-regulate intracellular pathways resulting in β-catenin accumulation that along with the activation of other regulators lead to the expression of osteoblastic genes [33]. Dkk-1 secreted by myeloma cells contributes to increased osteoclastogenesis by changing the ratio of OPG and RANK [33] [34]. Increased levels of Dkk-1 inhibit activation of the Wnt3a protein, resulting in reduced OPG expression and increased RANKL one, thus exacerbating osteoclastogenesis. High serum levels of Dkk-1 were associated with the presence of lytic bone lesions in MM patients in a study by Tian *et al.* who compared 45 MM patients with no bone lesions, as detected by MRI, to 137 with detectable lesions [35]. However, there was no correlation between Dkk-1 levels and severity of symptoms or disease activity [35]. Transgenic mice overexpressing Dkk-1, exhibit osteopenia,

Table 2. Published diverging results on serum OPG levels.

Author	#Pts studied	*Pts status*	Correlations found and/or comments
Goranova-Marinova (2007) [21]	66	At diagnosis	1. OPG levels higher in MM compared to HI 2. The OPG/creatinin ratio eliminated the difference 3. OPG levels correlared with b_2M and reversely with MBD*
Martini (2006) [22]	26	At diagnosis (smoldering myeloma)	OPG levels lower in MM compared to HI
Terpos (2005) [23]	35	Refractory (7) or relapsed (28) myeloma	1. OPG levels higher in MM before treatment compared to HI 2. The OPG/creatinin ratio eliminated the difference
Kraj (2005) [24]	133		1. OPG levels higher in MM compared to HI 2. OPG levels higher in pts with renal failure and hypercalcemia 3. OPG levels correlated with age, b_2M and bone marrow OPG concentrations
Depil (2005) [25]	140	At diagnosis 39 asymptomatic 101 mptomatic	1. OPG levels higher in MM compared to HI 2. No statistically significant difference between symptomatic and asymptomatic MM pts 3. OPG levels correlated with b_2M and creatinine 4. High OPG levels associated with a poorer survival
Corso (2004) [26]	103	39 at diagnosis 64 treated	OPG higher in MM and MGUS compared to HI.
Kyrtsonis (2004) [27]	32	27 at diagnosis 5 at remission	1. OPG levels higher in MM compared to HI OPG levels correlated with b_2M
Terpos (2004) [28]	51	4 at CR, 44 at PR 3 progressive/resistant	OPG levels lower in MM pre-ASCT compared to HI
Terpos (2003) [20]	121	At diagnosis	1. OPG levels lower in MM compared to HI 2. OPG levels correlared with b_2M, CRP and IL-6 levels, and inversely with MBD and serum markers of bone resorption
Seidel (2001) [29]	225	At diagnosis	1. OPG levels lower in MM compared to HI 2. OPG levels correlated with serum markers of bone formation and inversely with MBD and performance status

while reduced levels are accompanied by increased bone mass [36] [37]. Dkk-1 serum concentrations were also found to correlate with ISS staging in 50 patients, 32 at diagnosis and 18 pre- and post-autologous stem cell transplantation (ASCT) [38] and with the extent of MBD [39]. In our experience [40], serum DKK1 strongly correlated with the presence of spontaneous bone fractures, as shown in **Figure 3(a)** and **Figure 3(b)**. We had determined serum DKK1 by ELISA (human DKK-1, Duoset, R & D Systems) in 75 MM patients at diagnosis, including 11, 21, 21 and 22 patients with Durie and Salmon bone scale 0, 1, 2 and 3 respectively. No statistical difference was observed between serum DKK1 levels in 14 healthy individuals and patients bone scaled 0 to 2, neither was serum DKK1 concentrations related to parameters of disease activity or with survival.

1.2.3. Macrophage Inflammatory Proteins

Macrophage inflammatory protein 1a and 1b (MIP-1a, MIP-1b) are osteoclastogenesis inducing chemokines that participate in the pathogenesis of osteolytic lesions [41]. Albeight the ambiguous findings showing a role of MIP-1a on myeloma cells survival and growth [42] [43], its critical role on MBD is crearly outlined. MIP-1a promotes osteoclastogenesis and bone resorption either directly by acting on pre-osteoclasts or indirectly enhancing the activity of RANKL on osteoclasts and the activity of IL-6 [44]-[47]. High serum MIP-1a levels in MM patients were assosiated with extensive bone disease and degreased life expectancy (<3 years) [48]. However, the positive correlation between MIP-1α and β2-microglobulin in MM patients at diagnosis further supports

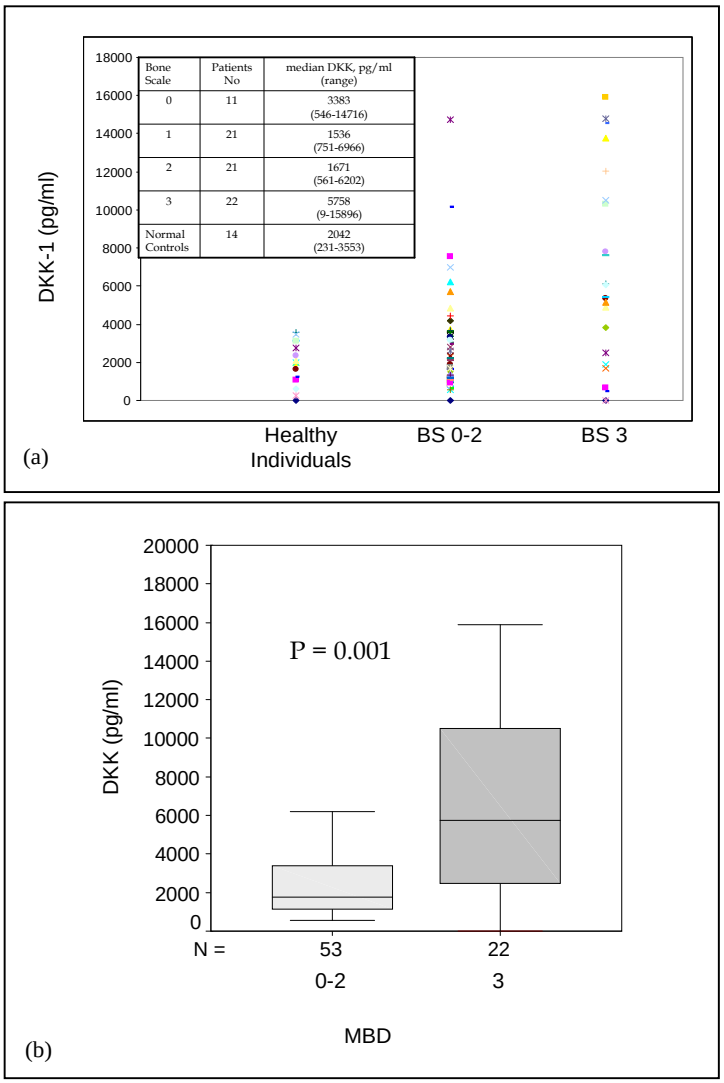

Figure 3. Correlations of serum Dkk-1 levels with myeloma bone disease.

the idea that MIP-1α is not only a chemokine involved in bone resoption but is also tangled in myeloma cell growth and survival [49]. In aggreement with the last, we also found that serum MIP-1α determined in 82 MM patients at diagnosis by ELISA (Quantikine, Human MIP-1a, R&D Systems, Minneapolis, USA), was related to markers of disease activity. Likewise, it mainly correlated with beta2-microglobulin (Spearman's rho 0.45, p = 0.0002) and consequently with ISS stages; MIP-1a levels were 28.3 ± 11.3 in ISS stage 1, 29.8 ± 11.1 in ISS stage 2, 39 ± 19.2 in ISS stage 3 (p = 0.02) [50]. With regard to MBD, MIP serum levels were lower in patients scaled 0 - 1 according to Durie and Salmon's bone scale in comparision of those scaled 2 - 3 with corresponding mean concentrations of 45.59 versus 65.03 pg/ml (p = 0.01).

1.2.4. Insulin Growth Factor-1 (IGF -1)

IGF-1, produced by bone marrow stromal cells and osteoblasts, contributes to myeloma cell survival [51]-[56]. IGF-1 and its receptor are preferentially expressed by MM cells [57] as compared to B-lymphoblastoid cell lines. IGF-1 serves as a chemoattractant for neoplastic plasma cells cells [51]. It augments the proliferative and anti-apoptotic effects of IL-6 [58] [59] and may have an equally important proliferative and anti-apoptotic effect as IL-6 on myeloma cells [60]-[62]. It was furthermore shown to be a strong indicator of prognosis in MM patients [63]. Interestingly, IGF-1 may contributes to the correlation of obesity and diabetes to neoplasia [64]. Because IGF-1 was involved in eventual down-regulation of osteoclasts, we investigated in 61 MM patients, studied at diagnosis, wether its serum levels correlated with MBD but no statistical significant relationship was found.

1.2.5. Other Cytikines Implicated in MBD

Osteoclasts are further regulated in MM by numerous osteoclast-activating factors (OAF) that include TNF-α, IL-1, IL-6 and other soluble molecules. In addition because cell to cell contact between OC and plasma cells activates both cell types, any factor that sustains myeloma cell survival and proliferation, including endothelial cell mitogens, will indirectly promote MBD. The report of all these factors, in the present context would be fastidious to the reader and will be skipped.

1.3. Treatment

Treatment of skeletal manifestations in MM requires management of the underlying malignancy but improvement of bone pains with chemotherapy may be delayed for one or two months and may be unbearable; so palliative analgesia may be required. In addition, the risk of spontaneous fracture significantly increases around the time of diagnosis [64], and adjuvant inhibition of bone resorption with aminobisphosphonates or eventually newly manufactured monoclonal antibodies is mandatory. Furthermore, in case a spontaneous fracture has already happened, at the time of diagnosis (or afterward), or that spinal cord compression symptoms occur, emergency treatment is needed in order to avoid devastating complications. Therefore MBD treatment can be subdivided into palliative, adjuvant and emergency therapy, indeed without omitting underlying MM treatment.

1.3.1. Myeloma Treatment

Because of the close relationship between myeloma plasma cells and osteoclasts, any treatment that will control and decrease plasma cell proliferation will also lead to decreased osteoclast activity and subsequently of MBD improvement.

Myeloma therapy has consistently improved over the last years. According to patient's age and disease aggressiveness, induction treatment upon diagnosis of symptomatic disease can include a combination of alkyliating agents (melphalan or cyclophosphamide), new agents, eventually anthracyclins and almost always corticosteroids; then after response, high dose treatment with autologous stem cell transplantation should be offered to younger patients. The so called new agents (thalidomide, lenalidomide, bortezomib and the new generation of ImiDs and proteasome inhibitors), introduced in the past 2 decades, have revolutionized myeloma therapeutics and resulted in improved outcomes [65] [66] and complete remission rates that were never observed before. Among these drugs, bortezomib has an osteoblast activating effect as it normalizes indices of bone remodeling, increases bone-type alkaline phosphatase and reduces serum dickkopf-1 [67]. Lenalidomide also was shown to reduce bone resorption in responding patients with relapsed/refractory multiple myeloma [68]. However, it should not be forgotten that these agents are administrated in combination with dexamethasone, the long term ingestion of which may increase osteoporosis.

1.3.2. MBD Palliative Treatment

Palliation of pain is a significant issue to deal with as it has serious impact on patient's quality of life. Therefore, proper use of analgesia is needed. Steroids procure an immediate relief of pain. Light narcotics may be of help until pain is controlled by chemotherapy or radiation. Nonsteroidal anti-inflammatory Drugs (NSAID) should always be prescribed with caution, as they may exacerbate myeloma related renal injury. Moreover, the temporary use of back braces or spinal orthotics to stabilize the spine or the thoracic cage, provide a short term relief of pain as axial pain is a common and annoying clinical finding reflecting not only loss of structural integrity but an impending spontaneous fracture too. Additionally, orthotics may be rather helpful in the early stages of remobilization after treatment. Typically, orthotics should not be used for a long period as their use is supplementary.

Radiation Therapy can be considered for palliative treatment [69]. Pain relief is often achieved within one or two fractions of 3 - 4.0 Gy [69] [70]. Radiotherapy should be recommended as a primary treatment for peripatetic patients with no risks of impending spinal fracture [71]. If possible, radiation therapy should be avoided in bone marrow producing areas before stem cell collection, in candidates for high dose treatment and autologous stem cell transplantation.

Other palliative techniques for myeloma-related spine pains are vertebroplasty and kyphoplasty. The aforementioned procedures are techniques indicated for low energy vertebral fractures either due to diffuse osteoporosis or to extensive osteolytic lesions. Vertebroplasty is the technique in which bone cement is injected percutaneously, under fluoroscopy, into the fractured vertebral body [72]. Balloon kyphoplasty may be considered as a modification of vertebroplasty; it requires the use of an expansible balloon into the vertebral body restoring that way its height [72]. The theoretical advantages of kyphoplasty over vertebroplasty are the ability to correct the kyphotic angle deformity and the reduced risk of adverse events such as cement leakage. The two techniques achieve pain relief in about 90% of patients [73]-[75]. Rare complications include inflammation, epidural hematoma, rib fractures, cement leakage, pulmonary embolism and systemic toxicity. Absolute contraindications involve bleeding disorders, infection, any contraindication to anesthesia, cord compression, severe cardiopulmonary insufficiency while relative ones include lesions above the level of T3, osteoblastic type of lesions, age below 40 years old, and fractures with obstructing and retropulsed bone [72] [76].

Kyphoplasty was included in the International Myeloma Working Group indications for painful vertebral compression fraction (more than 7/10 on visual analog scale), in patients with significant loss of vertebral height and prolonged life expectancy [76].

Seventeen patients followed and treated in our section, with a total of 43 vertebral fractures or significant osteolytic lesions were treated with kyphoplasty. Through minimal incisions, two special inflatable balloons were transpedicularly or extrapedicularly inserted and inflated in each treated vertebrae. After appropriate inflation of the balloons a certain degree of reposition of the Vertebral Compression Fracture (VCF) was obtained. Consequently a proper amount of polymethylmethacrylat cement was injected in every vertebra. Deformity correction was evaluated using standard calculation formula based on the fractured vertical height pre and post operatively. Pain degree was estimated before and after the procedure using the VAS score. All 17 patients tolerated the procedure well; they were discharged ambulatory the following morning of the procedure. In 23% of the VCFs, the deformity correction achieved 90% of the vertebral body height restoration, in 61% resulted to 60% - 89% restoration and for rest, the reduction was measured as 30% - 59%. Six months later the correction was stable. For a median follow up time of 18 months (range 4 - 30) there were no early or late complications related to the technique as cement extravasations, relapse of the MM in the same VB or even refracture. All patients experienced immediate and stable pain relief (median VAS pro-post: 6 - 1) and improvement in the quality of life (**Figure 4**).

Harrington in 1986 and later Mirel proposed scoring systems for decision making in impending pathologic fractures [77] [78]. Hip and periacetabular lesions, impending or pathological fractures of the acetabulum and long-bone fractures or any extensive skeletal destruction that may cause decreased quality of life, with increased pain and limitations in function and mobility, should be considered for surgical procedure [79] [80]-[82]. Prosthetic replacement is suggested for extensive hip lesions, pre operative radiation and total hip arthroplasty with acetabular reconstruction with or without reinforcement, depending on the extend of lesion, are suggested too (**Figure 5**); intramedullary devices over plates for lesions in the sub-trochanteric region [77]. Proximal femoral replacement should be considered in selected cases [77].

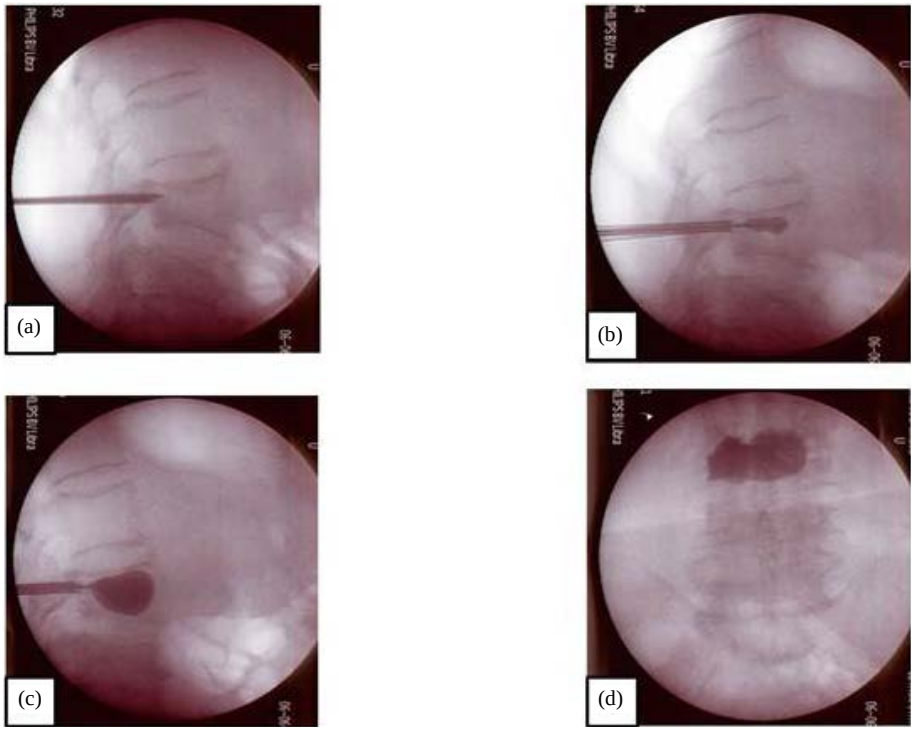

Figure 4. Ballon kyphoplasty. (a) Insert instrument in the fractured vertebra body; (b) Insert balloon Tamp; (c) Inflamation of the ballon and cement injection; (d) AP view just postoperatively.

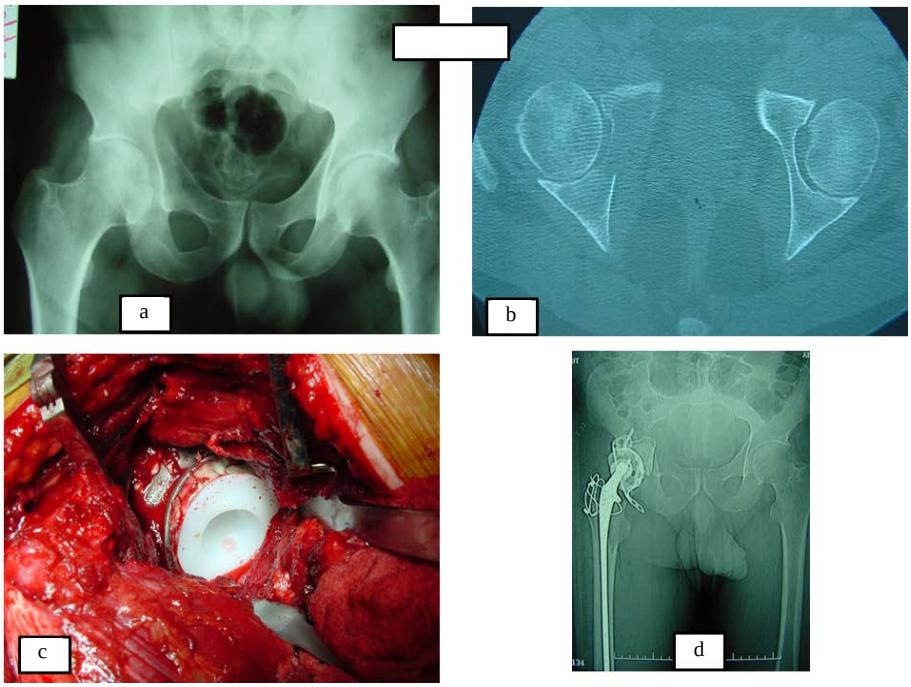

Figure 5. Anteroposterior radiographs of the hips of a 44-year-old man with multiple myeloma. (a) Class II lesion of the right acetabulum; (b) CT scan view of the lesion; (c) Right total hip arthroplasty with reconstruction of the acetabulum using an antiprotrusio cage, methylmethacrylate and screws fixed into the ilium; (d) The patient had a satisfactory result. Anteroposterior radiograph at 6 months follow up.

1.3.3. Inhibition of Bone Resorption

In current practice, aminobisphosphonates (pamidronate or zolendronic acid) are administrated in almost all symptomatic MM patients with an acceptable renal function, concomitantly to chemotherapy, in order to prevent skeletal related manifestations.

Biphosphonates (BPs) are inhibitors of osteoclast-mediated bone resoption. Moreover, nitrogen-containing BPs suspend the osteoclastogenic signaling pathway [83]. They are also used for the management of disease-related hypercalcemia. They may have an additional antitumor activity including effects on MM cells proliferation, apoptosis and adhesion [84]-[89] immunomodulatory and anti-angiogenic properties [90]-[92] and a regulatory role on drug resistance [93] [94].

The I.V administration of aminibisphosphonates monthly in the daily clinical practice has reduced skeletal related events at a remarkably lower level than before [95]. The optimal length they should be given is not fully determined yet but it is clear that treatment should continue for at least two years [96].

Risk of developing osteonecrosis of jaws and renal impairment are the most important clinical safety considerations [97]. In all patients creatinine clearance (CrCl), serum electrolytes, and urinary albuminmust be closely monitored [96] and careful dental evaluation is mandatory before aminibisphosphonates prescription [98]; Calcium and vitamin D3 supplementation can be used with caution to maintain calcium homeostasis.

Other antiresorptive therapies are emerging, inhibiting osteoclast function by affecting biological pathways that regulate osteoclasts' recruitment, activation, and function. The anti-Dkk-1 monoclonal antibody, denosumab is currently under evaluation in MM patients and has already proven its efficacy in postmenopausal osteoporosis [32]. Preliminary results are encouraging, while it also seems to confirm, *in vivo*, its potential pro-anabolic and anti-MM effect [99] [100]. Another antibody that was recently manufactured is romosozumab, an antibody against sclerostin, that in turn negatively regulates osteoblasts and inhibits bone formation; this drug (AMG 785) appears extremely potent [101].

1.3.4. Emergency Treatment

Spinal cord compression is an emergency situation. The usual primary management involves high-dose corticosteroids and radiation therapy. Surgical decompression may be considered as the choice to follow even though literature provides many controversial studies on when it is the appropriate time to proceed. Early studies on laminectomy had been abandoned as they did not present significant benefit over radiotherapy alone [102]. In a meta analysis study, Klimo *et al.* has presented the effectiveness of spinal decompression followed by immediate stabilization [103]. As most myelomatous lesions arise from the vertebral body, an anterior surgical approach is generally used, which may contribute to additional morbidity [71] but this is controversial and others support that direct decompressive surgery in combination with postoperative radiotherapy is superior to radiotherapy alone [104].

2. Conclusion

Multiple myeloma has the highest incidence of skeletal manifestations among malignant haematologic diseases. Albeit pain is the predesponsing symptom in approximately 60% of the symptomatic patients [4], spontaneous fractures, diffuse osteoporosis and spinal cord roots compression symptoms are additional clinical findings at diagnosis and throughout disease courses that lead to increased morbidity [1] [5]. Therapeutic strategy includes myeloma-directed chemotherapy, agents inhibiting bone resorption such as aminobisphosphonates and new promissing biology driven monoclonal antibodies targeting osteoclastogenesis mechanisms. Palliative MBD treatment includes analgesics, orthotics, radiation therapy, vertebroplasty and kyphoplasty. In case of spinal cord compression, radiation therapy or surgical decompression, should be instantly performed, along with steroid administration. Surgery may also be an option especially in case of weight-bearing bone fractures.

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