MULTIPLE MYELOMA: CLINICAL ASPECTS OF BONE DISEASE*

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INTRODUCTION

Myeloma is a malignancy of plasma cells which accounts for 1% of all cancers and 13% of haematopoietic tumours. In an unselected Scottish population the incidence was 49 per 1,000,000, median age of onset 71 years and average survival only 18 months.[1]

The largest study of the prevalence of bone disease in myeloma was performed in the USA in the mid-1970s.[2] Bone pain was the commonest symptom in myeloma affecting 60% of patients. Eighty per cent of patients had radiological evidence of osteolysis at diagnosis, 60% had a fracture (usually vertebral) and 30% were hypercalcaemic. In a more recent study in the UK of 254 patients[3] similar figures were obtained. The commonest site of pain is the spine, although the ribcage, shoulder girdle and hips are frequently involved. Bone disease can lead to pathological fracture, spinal cord compression, hypercalcaemia and pain. Progressive vertebral collapse, if severe, can lead to respiratory impairment.

Strong opiate analgesics are often required (with their well-recognised, and not infrequently troublesome, side-effects). Whilst NSAIDs are useful in the management of bone pain, potential to precipitate or exacerbate renal failure is of particular concern in myeloma in view of the frequency of underlying renal damage.[4]

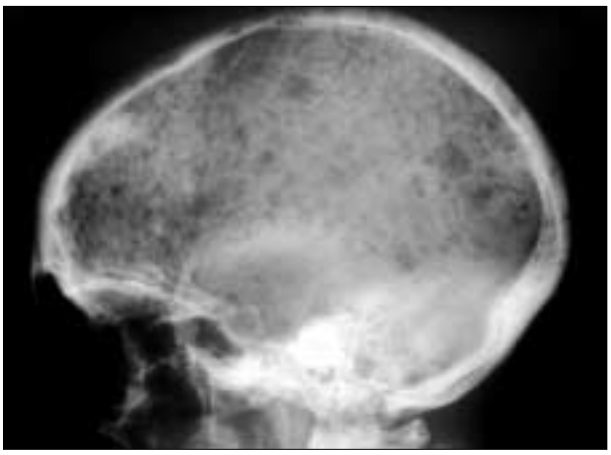

FIGURE 1
Skull X-ray showing numerous punched-out lytic lesions, typical of multiple myeloma.

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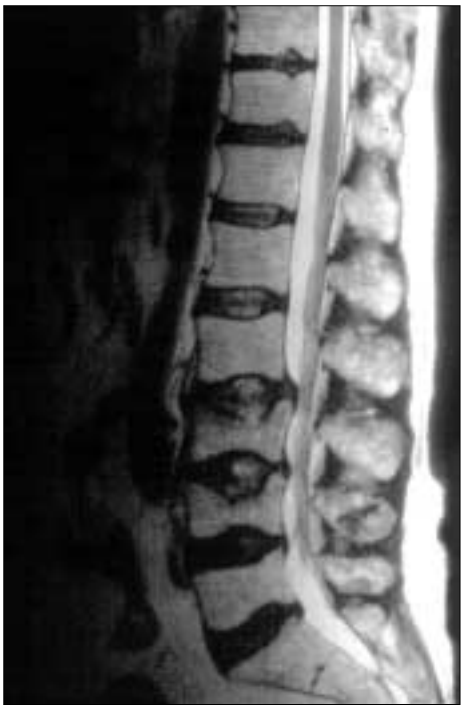

FIGURE 2
Sagittal T2 weighted MR image of the lumbar spine showing L3/L4 vertebral collapse, posterior disc herniation and indentation of the thecal sac.

Myelomatous bone disease represents an imbalance in bone resorption/formation. This imbalance occurs because of impaired osteoblast activity and increased osteoclast activation.[5,6] Osteoclast activation occurs in close proximity to the malignant plasma cells[5] and is due to the production of 'osteoclast activating factors'. Initially identified in the 1970s these factors are now known to be cytokines including IL-1β, TNF-β and possibly IL-6 (reviewed by Kanis and McCloskey)[7] produced in the bone marrow microenvironment by cells of tumour and non-tumour origin. A vicious cytokine cycle seems to exist with myeloma cells activating osteoclasts and osteoclasts stimulating myeloma cells. The latter is probably due to secretion from the osteoclasts of IL-6, a potent myeloma growth factor.[8] Inhibiting osteoclast activity might therefore control tumour growth, as well as bone resorption.

IDENTIFICATION OF MYELOMATOUS BONE DISEASE

Conventional radiology remains the most widely used imaging technique in myeloma. Although osteolytic lesions are common in patients with myeloma (Figure 1), osteopenia is often the only identifiable abnormality[9], and this cannot be differentiated radiologically from 'simple' osteoporosis. Magnetic Resonance (MR) imaging, however, offers greater sensitivity, identifying deposits in the spine of >90% of

patients with myeloma[10] (Figure 2). Unfortunately, access to MR scanning can be difficult; the procedure is relatively lengthy, only focuses on one part of the body and is contra-indicated in some patients.

Bone scintigraphy is generally less sensitive and specific than conventional radiology in the diagnosis of bone disease in myeloma,[9,11,12] probably because there is little reactive bone formation. Occasionally radionuclide images can become positive before radiological changes become apparent. Bone scintigraphy therefore has a role in evaluating the patient with myeloma who has bone pain and a negative X-ray where access to MR imaging is not feasible.

MEDICAL TREATMENT OF MYELOMA BONE DISEASE

Chemotherapy

Adequate chemotherapy is the mainstay of management in symptomatic myeloma. Conventional chemotherapy has a significant effect on bone pain with a reduction in the prevalence of moderate to severe pain from 75% at diagnosis to 15%, or less, for patients who reach 'plateau phase' i.e. respond to chemotherapy and achieve stable disease.[7] Rib and back pain appear to be more responsive than pain in the upper or lower limbs.[13] However, healing of bone lesions is unusual with conventional chemotherapy and skeletal disease generally progresses despite the attainment of stable disease as evidenced by other markers.[6]

Resorption-inhibiting drugs

A variety of resorption-inhibiting drugs have been used in myeloma. No benefit was found from either fluoride alone[14] or a combination of fluoride, vitamin D, calcium and androgen.[15] Recently, most interest has focused on the role of the bisphosphonates - pyrophosphate analogues in which the central oxygen is replaced by carbon. Bisphosphonates vary in their mode of action, and in their *in vitro* and *in vivo* potencies (Figure 3). Although a number of studies have been performed to evaluate the potential role of bisphosphonates in multiple myeloma (reviewed by McCloskey)[13] there are only four, large, placebo-controlled, double-blind, randomised trials.

In the first study[16] the use of oral etidronate (1-Hydroxyethylidene bisphosphonate) failed to reduce bone pain, episodes of hypercalcaemia, development of pathological fracture or loss of height. This has been attributed to the low potency of etidronate and its ability to concurrently inhibit bone mineralisation.

The Finnish Leukaemia Group[17] reported on the continuous daily use of 2,400 mg oral clodronate (Dichloromethylene bisphosphonate) in 350 newly-diagnosed, untreated, symptomatic patients. Radiologically clodronate significantly reduced osteolytic progression after 24 months from baseline assessment (24 vs. 12%, p = 0.026). Although a favourable trend was noted there was no statistically significant effect on fracture rate, episodes of hypercalcaemia, pain index or analgesic use.

In 1996 Berenson *et al.*[18] reported on 392 patients with advanced myeloma who received the more potent, second generation amino bisphosphonate, pamidronate. The drug was given intravenously (which overcomes the notoriously poor absorption of oral bisphosphonates, <1-10%), four-weekly and analysed after only nine months of therapy. Skeletal events (defined as pathological fracture, irradiation or surgery to bone, and spinal cord compression) were

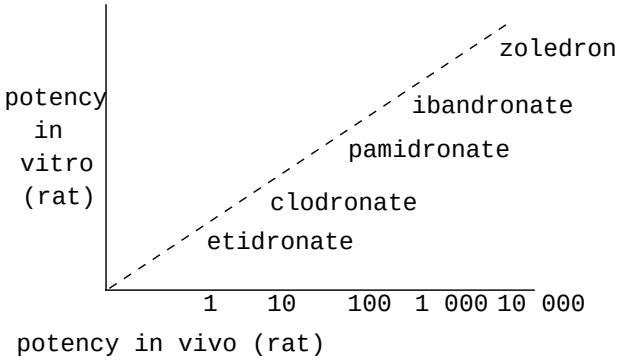

FIGURE 3
Relative potencies of the bisphosphonates.

significantly reduced compared with placebo (24 vs. 41%, p <0.001). Pain score significantly improved in patients treated with pamidronate, but not in controls. A score of analgesic use increased significantly in controls but not in patients treated with pamidronate. Performance status and quality of life were reported to significantly worsen in controls but not pamidronate-treated patients. However, no data were presented to support this. Pamidronate had no significant effect on overall survival or radiographic osteolysis. In a longer follow-up the beneficial effect of pamidronate was maintained.[19] In addition, in patients on second line (or greater) chemotherapy there is a suggestion that pamidronate prolonged survival.

In 1998 the British MRC published the results of using continuous oral clodronate within the context of the sixth MRC myeloma trial.[20] With 536 patients this is the largest trial examining the effect of a bisphosphonate in myeloma. Unlike the study of Berenson *et al.*[18] patients with early stage myeloma were also included. Daily clodronate use (1,600 mg) was associated with a significant reduction in non-vertebral fractures (7% vs. 13%, p = 0.04), vertebral fractures (38% vs. 55%, p = 0.01) and loss of height (2.0 vs. 3.4 cm, p = 0.01). The incidence of severe hypercalcaemia fell (5% vs. 10%) but just failed to reach statistical significance (p = 0.06). Back pain and performance status were significantly improved by clodronate at 24 but not six, 12 or 36 months from diagnosis. The lack of benefit from clodronate at six and 12 months may be because its effect was masked by the beneficial impact associated with the introduction of chemotherapy. Clodronate appeared to be most beneficial in patients without vertebral fractures at diagnosis and may have prolonged survival in this subgroup (median survival 1,362 vs. 1,094 days, p = 0.05).

These trials clearly demonstrate the advantageous effect of either clodronate or pamidronate in multiple myeloma. However, several questions are immediately generated:

1. Which bisphosphonate should be given and in what dose?
2. Should all patients with myeloma receive a bisphosphonate or only a selected group based on stage or natural history of the disease in the individual patient?
3. In view of the expense, what about cost/benefit?
4. Can treatment be tailored to individual patients?

1. Unfortunately, the pamidronate and MRC trials are not directly comparable, principally in terms of the patient's stage of myeloma. Comparative trials of clodronate and pamidronate in the setting of hypercalcaemia are limited,[21,22] involve small patient numbers and are hampered by assessing equivalent doses. In addition the differing modes/ease of administration may influence prescribing preference. Costs of oral clodronate and i.v. pamidronate seem to be similar. It is therefore not possible to give an evidence-based opinion of whether pamidronate is superior to clodronate, or vice versa, in the management of myeloma.
2. Recent American guidelines[26] recommend bisphosphonates only for myeloma patients who have bone disease and advocate that patients without bone disease should receive a bisphosphonate only in a research setting. This guideline, however, did not include the recent MRC trial[20] in its literature review. The MRC study, and the fact that bone resorption can be detected histologically months or years before radiology,[23] supports the early use of bisphosphonates in myeloma, and in patients of all stages. In addition the potential anti-tumour effect of bisphosphonates, if proven, would support their early (and long-term) use. Guidelines for treatment of myeloma in the UK are in preparation and will address the issue of bisphosphonate use and will have the advantage of being able to include the MRC data in their analysis.
3. The Finnish clodronate study undertook a cost/benefit analysis[24] and, perhaps surprisingly, found no additional total treatment cost from the use of clodronate. As the two subsequent trials[18,20] found a greater effect from bisphosphonate use one would expect that cost/benefit analysis of these studies would be encouraging. However, recent analysis of the MRC clodronate study[25] found that prophylactic clodronate increased treatment costs, on average, by £3,377 per patient (17% of total treatment cost). No economic impact study appears to have been undertaken in the pamidronate trial reported by Berenson *et al.*[18]
4. As physicians we generally manage therapy (especially expensive therapy) depending on response. It seems logical to attempt to do the same with bisphosphonates. Theoretically this could be performed by following bone density and/or markers of bone resorption. Presently, however, lack of knowledge about the natural history of bone density in myeloma, limited access and logistics of performing bone densitometry and lack of specificity of bone resorption markers make this a dream rather than a possibility.

Finally, it should be stated that bisphosphonates also play a major role in managing myeloma-associated hypercalcaemia and may also have an additional, acute, beneficial effect on bone pain.[7,27]

Radiotherapy in myeloma bone disease

Radiotherapy is an effective treatment modality in treating bone pain in myeloma. A single fraction of radiotherapy appears to be as effective as fractionated therapy.[28] Upper and lower hemi-body radiotherapy can be used for generalised bone pain. Although such an approach is associated with greater haematological toxicity than conventional radiotherapy, marked symptomatic relief is generally achieved (reviewed by Samson).[29] Upper and lower hemi-body radiotherapy is an under-explored treatment modality in myeloma and its exact role requires to be established.

Fractionated, as opposed to single dose radiotherapy (together with dexamethasone 4 mg, four times a day) is advocated for spinal cord compression to reduce the risk of radiation induced oedema.[29]

A small percentage of patients (<10%) with plasma cell tumours present with an isolated marrow tumour or 'skeletal plasmacytoma', with the spine being the commonest site. Although most of these patients will eventually develop multiple myeloma, local radiotherapy should be given with curative intent as median survival exceeds ten years.[30] In view of the high risk of progression to frank myeloma these patients require long-term follow-up. Development of multiple myeloma requires systemic therapy but appears to be associated with a better outcome than myeloma arising *de novo*.[30]

Surgical treatment of myeloma bone disease

Surgical intervention is required for pathological, or incipient, fracture with post-operative radiotherapy once wound healing is complete. In many instances the cause of pain is mechanical and orthopaedic intervention and stabilisation can have striking benefits.

Surgical intervention is almost certainly underused. In a recent large study of women with breast cancer and bone metastases, O'Donoghue[31] concluded that orthopaedic review would have been appropriate in 89% of episodes but was sought in only 46%; surgery would have been feasible in 65% of episodes but was carried out in only 31%; bracing would have been appropriate in 40% of cases but was carried out in only 18%. There is no reason to believe that orthopaedic referral practice is likely to differ between physicians treating breast cancer and myeloma.[32]

CONCLUSION

The treatment of myeloma has recently undergone major advances. An air of therapeutic and research nihilism surrounded myeloma in the late 1980s and early 1990s. There had been no major therapeutic advance, or improvement in outcome, since Alexanian introduced Melphalan in the early 1960s. However, during the 1990s it has become apparent that high-dose chemotherapy with haematopoietic stem cell rescue can improve survival in younger patients.[33] Improvements in supportive care, for example the introduction of the use of peripheral blood haematopoietic stem cells, has extended the upper age for such procedures.

For patients not suitable for high-dose chemotherapy, bisphosphonates represent the first major therapeutic advance since the 1960s. The likely introduction of more potent bisphosphonates[34] offers further future hope for patients with myeloma.

Parallel to these clinical advances there has been a dramatic increase in research output in myeloma, in terms of both clinical and laboratory research. For example, clinical research has shown that donor lymphocytes can restore remission in patients relapsing after allogeneic bone marrow transplantation, demonstrating the importance of host immunity in disease control.[35] Laboratory research has led to greater understanding of the role of cytokines and adhesion molecules in myeloma growth and bone disease. Bisphosphonates have been shown experimentally to act directly on myeloma cells as well as osteoclasts *in vitro* and can induce programmed cell death (apoptosis).[36] The apparent *in vivo* anti-myeloma activity of bisphosphonates[37] may therefore have at least two mechanisms. One, an indirect

action by inhibiting osteoclast-derived cytokine production and myeloma growth, and two, a direct effect on the malignant plasma cell itself.

Recently set up groups such as the UK Myeloma Forum (physicians) and the International Myeloma Foundation* (patients and carers) should help co-ordinate these clinical and scientific advances.

Although for most patients multiple myeloma remains an incurable disease, the last decade has produced significant improvements in survival and quality of life. Hopefully the next decade will be associated with development on a similar scale.

SUMMARY POINTS

- Bone pain is the commonest symptom in myeloma.
- Most patients with myeloma have radiologically-detectable bone disease.
- Conventional chemotherapy has a significant beneficial impact in pain control.
- Despite chemotherapy, bone healing is rare and skeletal disease progresses.
- Bisphosphonates can help control myelomatous bone disease.
- Most, if not all, patients with myeloma should receive a bisphosphonate.
- Optimum management of myelomatous bone disease requires collaboration between haematologists, radiotherapists and orthopaedic surgeons.

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*The International Myeloma Foundation is a patient support group dedicated to education, treatment and research in myeloma. The European headquarters are sited at 9 Gayfield Square, Edinburgh, tel: 0131 557 3332.

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