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Problems monitoring response in multiple myeloma

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Abstract

There has been a revolution in the treatment of multiple myeloma over the past decade. This article seeks to correlate advances in imaging with advances in treatment and to highlight how proper understanding of both is necessary for optimum management.

Keywords: *Multiple myeloma; imaging; treatment.*

Introduction

Multiple myeloma is the second most common form of haematological malignancy in the Western World after non-Hodgkin's lymphoma, accounting for approximately 10% of haematological malignancies and 1% of all malignancies. It is a disease of later life with 98% of patients aged 40 or older. The aetiology is unknown though there is an increased risk in those who have a past history of radiation exposure.

Multiple myeloma is characterised by uncontrolled proliferation of plasma cells within the marrow (mature antibody producing B cells). This leads to disruption of the subtle balance between osteoblastosis and osteoclastosis within bone by overproduction of tumour necrosis factor-related induced cytokine (TRANCE) and inactivation of osteoprotegerin resulting in unrestricted osteoclastic activity manifest as lytic deposits. An unwanted secondary effect is the promotion of further clonal proliferation of myeloma cells further augmenting the disease process^[1].

Diagnosis is based on laboratory and radiographic findings and depends on three abnormal results:

- bone marrow containing more than 10% plasma cells (normally no more than 4% of the cells in the bone marrow are plasma cells)
- generalised osteopaenia and/or lytic bone deposits on plain film radiography

- blood serum and/or urine containing an abnormal protein.

In about 75% of all cases of multiple myeloma the paraprotein present (M protein) will correspond with one type of immunoglobulin. In about 60% of cases an abnormal protein, known as Bence-Jones protein may also be found in the urine. Measuring the amount of paraprotein in the blood or urine is of value in the diagnosis of myeloma and in monitoring the response to treatment.

Staging

The clinical staging system devised by Durie and Salmon distinguishes different patient subgroups in terms of tumour mass and disease aggression and still often determines management^[2]. Patients with at least two lytic foci are classified in advanced disease subgroups and aggressive systemic treatment is usually indicated. However, this staging system has recently been replaced by one based entirely on serum β_2 microglobulin and serum albumin levels^[3] (Table 1). Although patient outcome is affected by abnormalities of chromosome 13 it does not add to the prognostic power of the new international staging system^[3,4].

Table 1 *New international staging system*^[3]

Stage I	Serum $\beta 2$ microglobulin <3.5 mg/l
Stage II	Serum albumin ≥ 3.5 g/dl Not I or III ^a
Stage III	Serum $\beta 2$ microglobulin ≥ 5.5 mg/l

^aThere are two categories for stage II: serum $\beta 2$ microglobulin <3.5 mg/l but serum albumin <3.5 g/dl or serum $\beta 2$ microglobulin 3.5–5.5 mg/l irrespective of the serum albumin level.

Therapy

The International Myeloma Foundation and UK Myeloma Forum (with the support of the British Committee for Standards in Haematology) should be regarded as the preferred source of detailed guidance on treatment^[5,6]. Treatment strategy is directed towards adequate analgesia, rehydration, management of hypercalcaemia and renal impairment, and treatment of infection. The response categories (complete, near complete, partial, minimal, stable and progressive) are determined primarily by the level of M protein present. M protein is the level of monoclonal protein measured by protein electrophoresis in serum or 24 h urine. Changes in M protein should be supported with other evidence of treatment benefit to confirm response^[5].

Chemotherapy is indicated for management of symptomatic myeloma. High dose therapy using melphalan and prednisolone can produce complete remission in up to 75% of patients^[7,8]. In recent years thalidomide (and its more potent immunomodulatory analogue lenalidomide) has been recognised as a valuable drug for the treatment of myeloma^[9,10]. Other new agents entering clinical trials include conventional drugs (Doxil), cytokines (Avastin), biological agents (Betathine) and agents such as arsenic trioxide^[10–12].

The most serious morbidity in these patients arises from destructive bone deposits which cause severe intractable pain and pathological fractures often resulting in deformity and disability. Vertebroplasty and kyphoplasty have been performed to alleviate bone pain from collapsed vertebrae and restore vertebral body height^[13–15]. The introduction of the bisphosphonate group of drugs has transformed this aspect of the disease. They bind to bone at sites of active bone remodelling and can therefore inhibit myelomatous bone damage arresting the destructive cycle described above^[16,17]. These agents (used in conjunction with cytotoxic chemotherapy) have been found to be superior to chemotherapy alone in decreasing the incidence of pathological fractures and bone pain and may lead to prolonged survival^[18–21].

Autologous transplantation has an established place in the treatment of myeloma. It is the treatment of choice for patients aged under 65 and can be considered in older age groups (with good performance status) carrying a procedure related mortality of less than 5%^[10,22,23]. At present the added benefit of double or tandem

transplantation versus a single autologous transplant is not known.

Radiation therapy is reserved for patients with spinal cord compression secondary to vertebral body collapse associated with a soft tissue mass or pathological fractures elsewhere associated with a soft tissue mass. It can be very effective but permanently destroys normal bone marrow stem cells in the treatment field.

Myeloma is generally considered incurable. It is a slowly progressing disease with long periods of relative inactivity. Relapse occurs in virtually all cases. On current treatment regimens patients younger than 70 years can expect a median survival of 5 years (depending on stage)^[7,12]. Death results from bacterial infection, renal insufficiency and thromboembolism.

Side effects of therapy and complications: the role of radiology

Drug therapy

Infection is the single most dangerous complication for myeloma patients with the patient most at risk in the first 3 months of front-line therapy^[5]. Myeloma is associated with a higher incidence of infective discitis and cerebritis in part due to cytotoxic therapy induced immunosuppression associated with corticosteroid therapy^[24–26]. Central venous catheters represent a potential source of bacteraemia^[27]. Magnetic resonance imaging (MRI) enables early identification followed by percutaneous needle aspirate using computed tomography (CT) to confirm the diagnosis and provide information regarding choice of antibiotic^[28]. Melphalan is associated with increased pancytopenia, mucositis and pulmonary complications^[29–32]. Plain film radiography and CT scanning are the appropriate imaging investigations. High doses of corticosteroids may cause spinal fractures and avascular necrosis of the femoral heads (amongst other bones). MRI is useful for assessing both these conditions. When thalidomide is used in combination with dexamethasone it carries a 16% incidence of deep vein thrombosis (DVT)^[33,34]. Abdominal discomfort resulting from constipation is also a well-recognised side effect of thalidomide and can be readily assessed radiologically using a supine plain radiograph of the abdomen. A recently reported side-effect is interstitial pneumonitis which can be identified on high resolution CT^[35]. The newer class of drug Bortezomib (a proteasome inhibitor reserved for relapsed disease) is associated with cytopenia and a decrease in platelet count to $<50\,000$ mm³ occurs in almost 30% of patients increasing the risk of haemorrhage^[36]. This drug has not been associated with an increased incidence of DVT in trials conducted to date^[12]. Chronic bisphosphonate use is associated with renal damage (monitored with regular serum creatinine levels) and osteonecrosis of the mandible^[37,38]. Regular dental check-ups in association

with an orthopantomogram enable early diagnosis of the latter.

Marrow transplantation

Allogeneic transplant is a high risk procedure with reported mortality of 15%–20% in the best centres due primarily to infection and graft vs. host disease^[39,40]. Encephalopathic changes (which are reversible) may develop as a result of cyclosporin therapy^[41]. In patients undergoing non-myeloablative or 'mini' allogeneic transplants there is a high risk of acute (32%–39%) and chronic (32%–46%) graft versus host disease in reported series^[10]. Imaging depends on symptomatology and consists of plain film radiography, CT and MRI as required.

Complications

Spinal cord compression resulting from vertebral body collapse may occur in up to 25% of patients and has been described as the presenting feature in 12% of patients^[42–44]. Early recognition of back pain and neurological symptoms is essential. Magnetic resonance is the imaging investigation of choice. Pathological fractures are common, occurring in 50% of patients^[45]. Fractures of the tubular bones heal readily with normal amounts of callus but extensive fractures may require insertion of intramedullary nails. Myelofibrosis manifest by diffuse low signal on both T1 weighted (T1W) and short tau inversion recovery (STIR) sequences and amyloidosis manifest by focal areas of decreased signal on T1W and STIR sequences are other recognised complications^[46].

Renal impairment is common in myeloma and affects up to half of all patients at some stage in their illness. This is usually a consequence of amyloidosis rather than plasma cell infiltration^[47]. Other possible causes include hypercalcaemia, dehydration, hyperuricaemia, infection or the action of nephrotoxic drugs. Unfortunately several of the drugs that are used to treat myeloma have an adverse effect on kidney function. Secondary amyloid occurs in approximately 10% of cases and in the early stages ultrasound demonstrates enlarged kidneys with increased cortical reflectivity. Amyloid protein is deposited mainly in the cortex so that corticomedullary differentiation is preserved and the pyramids are normal in size^[48]. Radiolabelled serum amyloid P component scintigraphy is a non-invasive and quantitative method for imaging amyloid deposits though it is less effective in myeloma associated amyloid than other forms of amyloid^[49].

Radiology of responding/relapsing disease

The role of radiology in the assessment of treatment response is limited and sequential quantification of

biological markers of disease (monoclonal protein levels and bone marrow plasmacytosis) are usually sufficient to assess response to chemotherapy.

Anatomical imaging

Plain film radiography

Almost 80% of patients with multiple myeloma will have radiological evidence of skeletal involvement at diagnosis manifest in four different appearances: solitary deposit (plasmacytoma); diffuse skeletal involvement (myelomatosis); generalised osteopaenia; and sclerosing myeloma^[46]. The most common sites include the vertebrae, ribs, skull and pelvis, whereas involvement of the distal bones is unusual. In early stage disease the role of the plain radiograph is limited with myeloma deposits often not visualised^[50,51]. Myeloma lesions are sharply defined, small lytic areas (average size 20 mm) of bone destruction with no reactive bone formation. At post mortem these lesions are due to nodular replacement of marrow and bone by plasma cells. Although myeloma arises within the medulla, disease progression may produce infiltration of the cortex, invasion of the periosteum and large extraosseous soft tissue masses. The pattern of destruction may be geographic, moth eaten or permeated. Generalised osteopaenia may be the only bone manifestation of myeloma in up to 15% of patients. Vertebral body collapse is the usual manifestation of this subtype which should not be confused with non-myelomatous osteoporosis which occurs in many older patients. On plain film radiography shrinking or sclerosing deposits indicate a response to chemotherapy and/or radiation therapy. The addition of bisphosphonate compounds as antiosteoclast agents leads to bone strengthening which further accentuates these features. Persistence of radiological abnormalities should not be considered evidence of active disease, since they may represent residual osteolysis in the absence of plasma cell proliferation.

Computed tomography

A wide range of findings have been described in CT of myeloma. These include sharp, lytic foci of small and relatively homogenous size with no sclerotic rim, diffuse faint osteolysis, an angioma-like appearance due to the presence of thickened vertical trabeculae and expansile deposits^[52]. Myelomatous marrow often shows an abnormally high attenuation value compared with normal marrow. Discrete interruption of the cortical contour may be seen. CT can accurately depict the extent of associated soft tissue masses and can direct needle biopsy for histological diagnosis. In treated lytic deposits disappearance of soft tissue masses and reappearance of a continuous cortical contour and of a fatty marrow

content may be observed. The advent of multidetector CT (MDCT) provides more detailed information on the risk of vertebral fractures compared with plain film radiography and MRI^[53]. In patients who are severely disabled or who are unable to undergo MRI examination this is a useful alternative imaging technique^[54].

Magnetic resonance imaging

MRI is used routinely due to its high sensitivity and its ability to directly visualise bone marrow. The imaging patterns in multiple myeloma can be classified as normal, focal, diffuse and variegated^[55,56]. A more detailed discussion on the MRI patterns is presented elsewhere^[57]. The lack of specificity of the MRI patterns should be noted. The focal and diffuse patterns may be observed in both metastatic disease from primary solid tumours and in other haematological malignancies, especially lymphoma and leukaemia. Differentiation between red marrow hyperplasia secondary to anaemia, infection, malignant or treated marrow infiltration can be extremely difficult. Normal marrow heterogeneities may mimic the variegated pattern although in most cases high signal intensity on T2 weighted images and contrast enhancement help distinguish relevant small marrow abnormalities from normal haematopoietic foci that generally show intermediate signal intensity on T2 weighted images and no contrast enhancement on T1 weighted images.

Several criteria exist for differentiating benign from malignant vertebral body compression fractures^[58,59]. However, these should be applied with caution to patients with multiple myeloma as normal signal intensity within a compressed vertebral body on spinal MR images does not preclude the diagnosis of multiple myeloma. In a study of 224 vertebral fractures in patients with known multiple myeloma Lecouvet *et al.* found that 67% appeared benign on MRI and 38% of their 37 patients had benign fractures only at diagnosis^[60]. In patients with osteoporotic or post traumatic vertebral compression of recent onset MRI will usually show signal alteration that parallels one of the end plates, involves less than half of the vertebral body, does not extend to the pedicles and enhances homogeneously following intravenous contrast. Diffusion weighted MRI may also prove to be a useful method to apply to the differential diagnosis of compression fractures^[61].

Patients being treated for multiple myeloma may suffer acute back pain secondary to vertebral body collapse even after effective chemotherapy. This is due to resolution of the tumour mass that was supporting the bony cortex. Thirty-five new vertebral compression fractures were discovered on post-treatment MR images of 29 patients with multiple myeloma in remission^[62]. In another study, 131 vertebral compression fractures appeared in 37 patients with multiple myeloma after the onset of therapy^[61]. Conversely, progression of disease may also

be responsible for a new compression fracture and MRI may be useful in differentiating between these two clinical settings. It has been shown that patients with either normal marrow appearance or less than ten focal lesions on pre-treatment MR images had significantly longer fracture free survival than patients with more than 10 focal lesions or with diffuse patterns on pre-treatment MR images^[63].

Interpretation of post treatment MRI changes can be difficult as there is a wide spectrum of possible treatment induced changes on MRI depending on the pattern of bone marrow infiltration. There has also been little long-term follow-up of these patients. Although MRI is more sensitive than the skeletal survey it is often difficult to differentiate inactive from active disease. Changes in contrast enhancement between the pre and post treatment MR examinations have been studied. The lack of lesion enhancement or only a peripheral rim enhancement seen after treatment can be indicative of responsive deposits. Focal marrow lesions may remain identical or decrease in size^[62,64,65]. Local radiation therapy of focal complex deposits induces a rapid decrease in the soft tissue extension and appearance of presumably necrotic, avascular central areas within the deposit on T1 weighted images with a later decrease in lesion size^[66]. In diffuse marrow abnormalities, increased marrow signal is usually observed on post treatment T1 weighted images due to reappearance of fat cells within more hydrated cellular components. Conversion of a diffuse to a focal or variegated pattern is also frequent^[62]. Post treatment MRI of the bone marrow may provide important information for patients with equivocal clinical and laboratory results as well as for patients with non-secretory myeloma.

In patients with advanced disease stages treated with conventional chemotherapy, patients with normal MR findings at diagnosis have better response to treatment and a longer survival than those with focal or diffuse marrow abnormalities at MR imaging^[67]. This feature has not yet been assessed in patients treated with marrow transplantation. Patients undergoing therapy with thalidomide have more favourable outcomes (better overall survival rate and prolonged event free survival) with a normal post-treatment MRI than those with persistent focal deposits^[9].

After bone marrow transplantation, bone marrow generally has a high signal on T1 weighted images but focal residual deposits are frequent^[68]. The prognostic significance of these abnormalities is uncertain as patients with these residual abnormalities did not have a poorer outcome than those with normal post transplantation MRI scans^[69]. Increased marrow cellularity due to marrow stimulating factors and decreased signal due to marrow haemosiderosis resulting from repeated transfusions may also be present on post-transplantation MR images. Despite the superiority of MRI over radiographs for spinal and pelvic lesion detection, an MRI survey limited

to these areas may be less sensitive than the conventional skeletal survey which may detect deposits in the skull and rib^[70].

In patients with clinical relapse new focal deposits or an increase in size of deposits previously present can be identified with MRI. Conversion of a normal or variegated pattern to a diffuse pattern indicates severe relapse on follow-up MRI scans. MRI is also useful in assessing status of leptomeninges as abnormal enhancement representing tumour spread has been reported in 18 out of 1856 treated patients in one series^[71]. In patients with a solitary bone plasmacytoma MR screening of the spine and pelvis will usually reveal radiographically unsuspected deposits in up to 80% of patients thus suggesting true myeloma from the outset. This finding is associated with a poor response to localised radiotherapy and an earlier development of systemic disease than in patients with a negative MRI survey^[72].

High levels of serum beta 2 microglobulin correlate with a poor prognosis and remain the single most powerful determinant of outcome^[73]. No correlation between this finding and appearances on MRI has yet been demonstrated. Long term prospective studies are required to establish the significance and prognostic value of the different MRI patterns of marrow involvement and their correlation with various laboratory values particularly in patients undergoing transplantation.

Functional imaging

Conventional scintigraphy

Although abnormal tracer uptake has been shown to indicate residual activity on conventional skeletal scintigraphy, osteoblastic activity due to healing vertebral body fractures, fractures elsewhere in bony skeleton and drug therapy (particularly bisphosphonates) will also give rise to increased isotope uptake^[16,17,74]. ^{99m}Tc-methoxyisobutylisonitrile (^{99m}Tc-MIBI) has been shown to be superior to plain film radiography and skeletal scintigraphy in detecting bone and bone marrow involvement^[75-78]. Different patterns of ^{99m}Tc-MIBI uptake have been described with multiple myeloma (negative, diffuse, focal, combined focal and diffuse) and semiquantitative evaluation of these patterns showed a significant correlation with clinical status and stage of the disease^[79]. A negative scan in a patient with multiple myeloma indicates early stage disease or post treatment remission while the presence of focal uptake and/or intense diffuse bone marrow uptake suggests an advanced stage of active disease. A subsequent follow-up study involving 22 patients showed a significant correlation between the scintigraphic findings and clinical status post chemotherapy^[80]. However, evaluation of the treated patient using this tracer may be compromised if drug resistance is present. If this is manifest as Pgp expression, dual phase imaging (at 10 min and 4 h following

injection) helps differentiate but if Bcl-2 is expressed correlation with other imaging is necessary^[81].

FDG-PET

Positron emission tomography (PET) using the glucose analogue fluorine-18 fluorodeoxyglucose has also proved useful. In one series comprising 28 patients FDG-PET was true positive in almost 93% of the radiographically documented osteolytic deposits and demonstrated a greater extent of disease than plain film radiography in 61% of patients^[82]. Other studies have demonstrated its reliability in detecting active myeloma both within bone and at extramedullary sites and its ability to differentiate between new active disease and inactive (treated) sites^[83-85]. In a recent study involving 13 patients using FDG-PET, nine of whom had undergone therapy, PET proved superior to anatomical imaging in identifying sites of active residual disease^[86]. Patients showing no abnormal or decreased FDG uptake demonstrated clinical improvement. False negative results may occur due to limitations with spatial resolution resulting in deposits less than 0.5 cm not being detected. False positive results may arise from inflammatory changes associated with radiation or chemotherapy so at least 2 months should elapse post therapy before this study is performed. FDG-PET is also accurate in assessing disease status in patients with extraosseous myeloma (5% of all myeloma patients)^[84,87,88]. Although no study has been published to date using integrated PET/CT imaging this technique is likely to be complementary to plain film radiography and/or MRI as anatomical assessment of myeloma deposits will still be necessary. Interestingly, a recent study comparing MIBI with PET indicated that MIBI identified more disease sites^[89].

Conclusion

The wide variety of options now available for treating multiple myeloma means that the radiologist has to be ever more alert in differentiating imaging features due to side-effects and complications of therapy from those related to responding/relapsing disease. There is still an important role for the skeletal survey with MRI/MDCT being reserved for bones that require closer evaluation. The benefits of bisphosphonate therapy can be assessed using dual energy X-ray absorptiometry (DEXA) scanning. The increasing availability of metabolic imaging means that FDG-PET/CT is likely to play an increasing role particularly in assessing status of extramedullary disease.

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