# Multiple myeloma

## Introduction

Multiple myeloma is a common haematological disorder, accounting for 2% of all malignancies in the UK (Raluy et al, 2014). This disease affects the elderly, with 70% of patients being over 60 years of age at diagnosis, and has a higher incidence in Afro-Caribbean populations. Multiple myeloma is a B cell neoplasm, arising from an abnormal expanded plasma cell clone. Nearly all patients have a precursor condition known as monoclonal gammopathy of undetermined significance (Landgren et al, 2009). Approximately 1% of patients with non-immunoglobulin M (IgM) monoclonal gammopathy of undetermined significance progress to multiple myeloma per year (Kyle et al, 2002) and those with IgM paraproteins nearly always progress to lymphoma, with IgM multiple myeloma being rare.

The guidelines for diagnosis of multiple myeloma have been amended to reflect new insights into ultra high-risk asymptomatic multiple myeloma (Rajkumar et al, 2014). This article helps the general physician to diagnose multiple myeloma, request relevant diagnostic investigations in light of changes made to the diagnostic criteria and learn about current treatment paradigms as well as novel therapies currently in clinical trials for multiple myeloma.

## Clinical symptoms

Patients can present with a range of different symptoms from fatigue to classical CRAB (hyperCalcaemia, Renal failure, Anaemia, Bony lesions) criteria (*Table 1*). The diagnosis of multiple myeloma can be difficult to make, with patients visiting their GPs on average three times before referral to secondary care. Anaemia may be accompanied by low platelet counts or more rarely low total white cell counts. Single symptoms such as back pain are often non-specific, although when coupled with laboratory abnormalities such as leucopenia or hypercalcaemia have a much higher predictive risk of multiple myeloma (Shephard et al, 2015). It is therefore imperative to consider a diagnosis of multiple myeloma in patients presenting with back pain coupled with haematological abnormalities or CRAB criteria. Bone disease may also present with pain in other parts of the skeleton including the shoulder, hip, sternum or limbs.

Multiple myeloma can be suspected in asymptomatic patients with features including an elevated erythrocyte sedimentation rate, serum total protein levels, globulins or plasma viscosity, low albumin level (Bird et al, 2011), asymptomatic bone lesions identified on radiology (X-ray, computed tomography, magnetic resonance imaging or positron emission tomography), non-selective nephrotic range proteinuria, significant Bence Jones proteinuria or evidence of amyloid deposition.

Commonly, asymptomatic patients are diagnosed when a paraprotein (abnormal monoclonal protein) is detected in either the serum or urine (Bence Jones protein) when under investigation for other disorders. Further tests are then performed to define the disease subtype. *Table 2* gives the incidence of common presenting symptoms in patients with multiple myeloma (Nau and Lewis, 2008).

**Table 1. Symptoms of multiple myeloma**

| Symptoms of myeloma – CRAB criteria | Laboratory criteria |
|---|---|
| Hypercalcaemia – abdominal pain, constipation, thirst, confusion | Serum calcium level >0.25 mmol/litre above upper limit of normal or >2.75 mmol/litre |
| Renal impairment – fatigue, confusion as a result of uraemia | Creatinine clearance <40 ml/min or serum creatinine >177 µmol/litre |
| Anaemia – shortness of breath on exertion, palpitations, fatigue, lethargy | Haemoglobin >20 g/litre below normal range or <100 g/litre |
| Bony lesions – lytic lesions, osteoporotic compression fractures, pathological fractures, plasmacytomas | Abnormal bony lesions seen on positron emission tomography-computed tomography, computed tomography, skeletal survey |
| Other symptoms:<br>■ Hyperviscosity – confusion, retinal haemorrhage, neurological deficit as a result of raised intracranial pressure, gum and mucosal membrane bleeding, decompensated heart failure<br>■ Immuneparesis – recurrent bacterial and viral infections<br>■ Cytopenias – bleeding, bruising, infections<br>■ Symptoms of AL amyloid deposition – macroglossia, periorbital ecchymoses, arrhythmias, autonomic dysfunction | Other laboratory abnormalities:<br>■ Low immunoglobulin levels<br>■ Low albumin levels<br>■ Elevated erythrocyte sedimentation rate<br>■ Elevated total protein levels<br>■ Elevated plasma viscosity |

*CRAB = hyperCalcaemia, Renal failure, Anaemia, Bony lesions*

## Diagnostic criteria for monoclonal gammopathy of undetermined significance

Monoclonal gammopathy of undetermined significance is defined as the presence of an abnormal monoclonal paraprotein

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**Table 2. Incidence of symptoms in patients presenting with multiple myeloma**

| Presenting symptoms | Incidence (%) |
|---|---|
| Bony pain | 58 |
| Fatigue | 32 |
| Pathological fractures | 26 |
| Weight loss | 24 |
| Paraesthesia | 5 |
| Fever | 0.7 |
| Asymptomatic | 34 |

in the absence of other diseases such as multiple myeloma, AL amyloidosis and other B-cell lymphoproliferative disorders. IgG and IgA monoclonal gammopathy of undetermined significance can progress to multiple myeloma. IgM paraproteinaemias usually progress to lymphoplasmacytic lymphoma, and only rarely progress to IgM isotype multiple myeloma (Rajkumar et al, 2007). The diagnostic criteria of monoclonal gammopathy of undetermined significance are shown in *Table 3*.

The Mayo group has designed a risk stratification model in which risk is assigned based on paraprotein level (<15 g/litre or higher), IgG or non-IgG isotype, and normal or abnormal serum free light chain ratio. Patients with no abnormality are defined as low risk, those with one abnormality as low-intermediate risk, two abnormalities high-intermediate risk and those with all three abnormalities are defined as high risk disease. The overall risk of progression of high risk monoclonal gammopathy of undetermined significance to multiple myeloma is 58% at 20 years (Rajkumar et al, 2005). There is currently no evidence to suggest treating patients with monoclonal gammopathy of undetermined significance is beneficial (Berenson et al, 2010).

Patients with the following abnormalities should be followed up by haematology teams rather than in primary care as they are at greater risk of progression or developing complications:

- High risk monoclonal gammopathy of undetermined significance (IgG paraprotein >15 g/litre or IgA/M paraprotein >10 g/litre)
- Monoclonal gammopathy of undetermined significance of rare isotype (IgD or IgE)
- Rapidly rising paraprotein (absolute increase by 5 g/litre or 25% increase over 3 months)
- Bence Jones protein >500 mg/24 hours
- Light-chain only monoclonal gammopathy of undetermined significance – risk of renal impairment.

Patients with low risk monoclonal gammopathy of undetermined significance as defined below can be followed up in primary care, usually every 3–4 months and then 6–12-monthly if clinically stable:

- IgG M protein <15 g/litre
- IgA M protein <10 g/litre
- Asymptomatic patients
- Uninvolved immunoglobulins normal or low
- No other abnormal results (Bird et al, 2009).

**Table 3. International Myeloma Working Group definitions of monoclonal gammopathy of undetermined significance**

| IgM monoclonal gammopathy of undetermined significance | Non IgM monoclonal gammopathy of undetermined significance |
|---|---|
| Paraprotein <30 g/litre | Paraprotein<30 g/litre |
| <10% clonal lymphoplasmacytoid cell bone marrow infiltration | <10% clonal plasma cell bone marrow infiltration |
| No evidence of end organ damage as a result of lymphoproliferative disorder: hyperviscosity, anaemia, lymphadenopathy, hepatosplenomegaly | No evidence of end organ damage resulting from plasma cell disorder (CRAB criteria) or AL amyloidosis |

*CRAB = hyperCalcaemia, Renal failure, Anaemia, Bony lesions*

**Table 4. Updated diagnostic criteria for multiple myeloma**

| **Definition of multiple myeloma: presence of ≥10% clonal plasma cells or biopsy proven extramedullary plasmacytoma and one or more myeloma defining events:** |
|---|
| 1. Evidence of end organ damage as defined by CRAB criteria |
| 2. Evidence of one or more high risk biomarkers:<br>■ >60% plasma cell bone marrow infiltration<br>■ Involved:uninvolved serum free light chains ratio >100<br>■ More than one abnormal focal bony lesion on magnetic resonance imaging (>5 mm size) |
| Asymptomatic or smouldering multiple myeloma – both criteria must be met:<br>■ IgG or IgA serum paraprotein >30 g/litre or urinary monoclonal paraprotein >500 mg/24 hours and/or clonal plasma cells 10–60% infiltration on bone marrow<br>■ Absence of myeloma defining events including high risk biomarkers or evidence of AL amyloidosis |

*From Rajkumar et al (2014). CRAB = hyperCalcaemia, Renal failure, Anaemia, Bony lesions*

## Defining myeloma

The International Myeloma Working Group diagnostic criteria for multiple myeloma are defined in *Table 4* (Rajkumar et al, 2014). Individuals with a paraproteinaemia are divided into three categories: monoclonal gammopathy of undetermined significance, asymptomatic or smouldering multiple myeloma, and symptomatic multiple myeloma. The risk of progression from smouldering multiple myeloma to symptomatic disease is 10% in the first 5 years but diminishes thereafter (Dispenzieri et al, 2008).

The new diagnostic criteria for symptomatic multiple myeloma identify three new biomarkers: >60% bone marrow plasma cell infiltration, abnormal serum free light chain ratio (involved to uninvolved ratio >100) and >1 abnormal focal lesion seen on magnetic resonance imaging. Patients fulfilling any of these criteria may be asymptomatic but have a high risk (80%) of progression to symptomatic myeloma within 2 years. In particular, the presence of >60% plasma cell infiltration has a high predictive value of progression with a median progression-free interval of 7 months (Rajkumar et al, 2014).

Owing to high risk of progression and development of complications, patients with these biomarkers are now treated in the same way as symptomatic patients and are now classified as having active multiple myeloma, whereas previously they would have been actively monitored until they developed symptomatic disease.

Imaging recommendations for detection of bony lesions have also been updated to include use of positron emission tomography-computed tomography and low-dose whole body computed tomography, as these techniques are superior to conventional skeletal survey. Substantial bone loss is required before multiple myeloma deposits are seen on plain films, whereas the alternative imaging techniques are more sensitive at detecting multiple myeloma-related bone disease (Regelink et al, 2013).

## Rare myeloma subtypes

Malignant plasma cells can produce different subtypes of monoclonal paraproteins. The most common subtypes are IgG or IgA paraprotein subtypes but IgD, IgE and IgM multiple myeloma can also occur (rare isotypes). Rare multiple myeloma subtypes make up only 7% of all multiple myeloma (Bird et al, 2011). Patients may also present with light-chain only disease (approximately 15% of patients) when the neoplastic plasma cell clone produces only abnormal κ/λ chains but no paraprotein (Magrangeas et al, 2004). Patients can also present with non-secretory multiple myeloma (2% of patients). These patients do not have detectable serum or urinary paraprotein but have an abnormal neoplastic clonal population of plasma cells present in the bone marrow (Drayson et al, 2001).

Rarely, patients can present with plasma cell leukaemia. This is defined as presence of ≥20% circulating plasma cells or an absolute value of >2x10$^9$/litre of plasma cells in the peripheral blood and can occur de novo or secondary to multiple myeloma. Plasma cell leukaemia is associated with a very poor prognosis, with a median survival less than 2 years.

## International staging system staging system for multiple myeloma

Once a diagnosis of multiple myeloma has been made, patients are staged according to the international staging system depending on their β2-microglobulin levels and albumin levels. The international staging system helps to prognosticate survival. Stage 1 disease (β2-microglobulin <3.5 mg/litre and serum albumin ≥35 g/litre) is associated with median survival of 62 months, stage 2 disease (disease that does not fulfil stage 1 or 3 criteria) 44 months and stage 3 disease (β2-microglobulin >5.5 mg/litre) 29 months (Kyle and Rajkumar, 2009).

The international staging system is not used for other plasma cell-related disorders or monoclonal gammopathy of undetermined significance. A revised international staging system score has been devised which combines adverse chromosomal abnormalities: 17p deletion, t(4:14) and/or t(14:16) and lactate dehydrogenase levels with β2-microglobulin and albumin for prognostication (Palumbo et al, 2015a).

## Investigations

In order to make a diagnosis of multiple myeloma the following investigations should be sent urgently:

- Full blood count – determine haemoglobin for CRAB criteria, neutrophil count to assess infection risk, platelet count to assess bleeding risk
- Renal function – determine creatinine level for CRAB criteria and assess need for dialysis
- Albumin and β2-microglobulin – not necessary for diagnosis, but required for staging
- Bone profile – determine calcium levels for CRAB criteria
- Serum and urine protein electrophoresis and immunofixation – identify presence of paraprotein or Bence Jones protein
- Serum free light chain levels – if serum paraprotein and Bence Jones protein absent, but multiple myeloma is suspected
- Total urinary protein – nephrotic range proteinuria can be seen in AL amyloidosis and non-selective proteinuria is seen in 15% of patients with multiple myeloma. Total urinary protein will also help to determine the extent of light chain deposition disease
- Serum lactate dehydrogenase levels – measure extent of proliferation (this is a requirement of the new revised international staging system staging criteria)
- Blood film – assessment of circulating plasma cells to make a diagnosis of plasma cell leukaemia.

The following tests are then usually requested by the haematology team:

- Bone marrow aspirate and trephine: aspirate-morphology to confirm diagnosis, cytogenetics and flow cytometry if concerns regarding diagnosis. Cytogenetic abnormalities such as t(4:14), t(14:16), t(14:20), chromosome 1q gain, 1p loss and deletion 17p are associated with a poorer prognosis
- Trephine – assessment of percentage of plasma cell infiltrate
- Imaging – computed tomography, positron emission tomography-computed tomography if available, or skeletal survey for osteolytic lesions. Magnetic resonance imaging of the spine and pelvis should be performed for all patients with asymptomatic myeloma.

It is beyond the scope of this article to discuss diagnosis and investigations for AL amyloidosis in depth. However, this diagnosis should be considered in patients with a paraprotein and the following symptoms: macroglossia, breathlessness, periorbital ecchymoses, weight loss, gastrointestinal disturbance, postural hypotension, autonomic dysfunction, lymphadenopathy, organomegaly, and significant non-Bence Jones protein proteinuria. Patients may have abnormal cardiac biomarkers (n-terminal pro B natriuretic peptide and troponin-T levels) which confer a poorer prognosis.

Diagnosis is usually made on biopsy of the affected organ using Congo red stain. This will classically show apple green birefringence under polarized light if positive. Approximately 50% of patients with amyloidosis have Congo red deposits on trephine biopsy. Subcutaneous fat pad aspirate can also be performed to confirm the diagnosis.

Patients are usually referred to the National Amyloidosis Centre at the Royal Free Hospital, London, for further specialist investigations and are managed jointly with local haematology teams.

## Treatment

Multiple myeloma is a disease with a classically relapsing remitting course. Patients may relapse with biochemical disease alone or with clinical symptoms. All patients should be treated in a holistic, multidisciplinary fashion. Patients should be given written information on their condition and introduced to a clinical nurse specialist.

**Table 5. Commonly used first-line therapies for multiple myeloma in the UK**

| First-line treatment options | Drugs used |
|---|---|
| Newly diagnosed multiple myeloma patients eligible for stem cell transplantation | ■ Bortezomib + dexamethasone + thalidomide<br>■ Bortezomib + dexamethasone + cyclophosphamide<br>■ Cyclophosphamide + thalidomide + dexamethasone (although bortezomib-based triplet regimens are more efficacious)<br>■ VDT-PACE (bortezomib + doxorubicin + thalidomide + cisplatin + cytarabine + dexamethasone + etoposide) and CVTD (cyclophoshamide + bortezomib + thalidomide + dexamethasone) can be used to treat plasma cell leukaemia |
| Newly diagnosed multiple myeloma patients not eligible for stem cell transplantation | ■ Attenuated CTD (CTDa) – cyclophosphamide + thalidomide + attenuated dexamethasone<br>■ CVD – bortezomib (if thalidomide contraindicated) + alkylating agent (cyclophosphamide) + dexamethasone on a 5-weekly schedule<br>■ MPT – mephalan + prednisolone + thalidomide<br>■ VD – bortezomib + dexamethasone doublet therapy may be appropriate |

All patients should be discussed in a multidisciplinary team meeting with clinical oncologists, pathologists, radiologists, haematologists and clinical nurse specialists, and a treatment plan formulated. If possible, the patient should always be offered participation in a clinical trial. Patients may need social and psychological support as well as specialist haematology care.

Patients with low risk asymptomatic multiple myeloma are actively monitored on a 3-monthly basis with a clinical history, examination, blood tests for full blood count, renal function, corrected calcium levels, serum paraprotein, urinary electrophoresis, urinary Bence Jones protein and serum free light chain analysis in light chain only disease or those with non-secretory multiple myeloma.

Patients with symptomatic multiple myeloma require cytoreductive therapy and are treated according to current National Institute for Health and Care Excellence guidance (*Table 5*). In principle, therapy is tailored to each individual based on his/her performance status, pre-existing comorbidities and symptoms. In younger fit patients standard of care involves induction chemotherapy with a novel agent followed by high dose autologous stem cell transplantation. Standard of care induction regimens are bortezomib and dexamethasone and/or thalidomide (National Institute for Health and Care Excellence, 2014) or cyclophosphamide, while the all oral regimen CTD (cyclophosphamide, thalidomide and dexamethasone) is a convenient alternative.

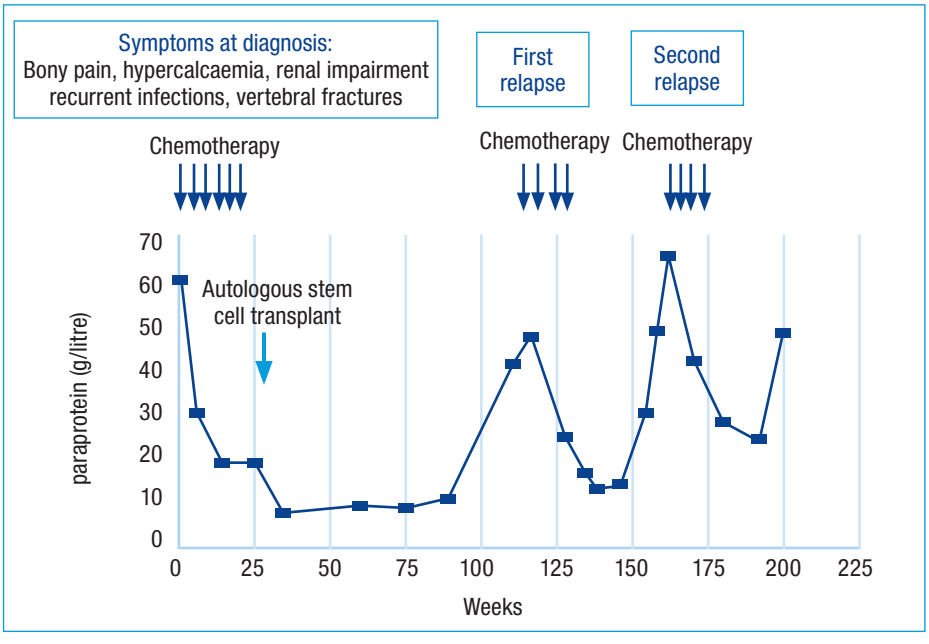
In older less fit patients not suitable for stem cell transplantation, standard of care first-line therapy is a regimen containing a novel agent, either thalidomide based: CTDa (attenuated CTD with lower dose dexamethasone), MPT (melphalan, prednisolone and thalidomide), or bortezomib based, in combination with melphalan and prednisolone or with cyclophosphamide and lower dose dexamethasone (National Institute for Health and Care Excellence, 2011). Lenalidomide, like thalidomide, is an immunomodulatory drug and is currently approved for treatment of patients at second relapse (National Institute for Health and Care Excellence, 2009), while bortezomib is also used to treat patients at relapse (National Institute for Health and Care Excellence, 2007). Ideally, elderly patients should have a frailty assessment score performed at diagnosis as this predicts survival and treatment-related toxicities (Palumbo et al, 2015b).

Chemotherapy is usually given in repeated cycles, each lasting between 3–5 weeks depending on the treatment regimen used and performance status. The patient's paraprotein and serum free light chains are monitored after each cycle to help assess response to treatment (*Figure 1*). Responses to treatment are graded depending on the magnitude of reduction in the paraprotein, Bence Jones protein or serum free light chains (e.g. complete or partial response). Common side effects of novel agent therapies are highlighted in *Table 6*. Patients should be assessed for side effects of treatment before commencing each cycle of chemotherapy and dose adjustments performed as necessary.

## Transplantation

In younger fit patients who have had a good response to treatment, an autograft is offered pending tests of kidney and cardiac function, and a successful stem cell harvest. Autologous transplantation is rarely considered curative but helps to deepen disease response and thus to delay disease relapse. Peripheral blood

**Figure 1. Natural progression of multiple myeloma in a patient fit for autograft.**



stem cells are harvested from the patient, usually after completion of 4–6 cycles of chemotherapy. These stem cells are then re-infused 24–48 hours after high dose chemotherapy (usually melphalan). Stem cell transplantation is usually an inpatient procedure requiring admission for 3–4 weeks. Patients require close monitoring, are at risk of bleeding, anaemia and febrile neutropenia (requiring broad-spectrum antibiotics), and often need frequent blood and platelet transfusions. On discharge, patients are monitored on a regular basis in outpatients, and have a repeat bone marrow biopsy assessment done at 100 days post transplant and then at 1 year post transplant to assess treatment response.

Following stem cell transplantation, patients are monitored for evidence of clinical or biochemical relapse. The use of novel agents as part of maintenance treatment is currently being evaluated (Wang et al, 2015). The Myeloma IX trial showed that thalidomide maintenance improved progression-free survival in patients without high risk disease, but not in those with adverse cytogenetics (Morgan et al, 2013). The HOVON trial has also shown improved complete remission rates, overall survival and progression-free survival in patients treated with bortezomib induction and maintenance (Sonneveld et al, 2012).

Tandem autografts are not routinely recommended outside of clinical trials. Allogeneic stem cell transplantation is not standard of care, and is usually only recommended in young fit patients with an HLA-matched donor, ideally in the context of a clinical trial (Bird et al, 2011).

**Table 6. Mechanism of action and side effects of novel agents and dexamethasone**

| Drug | Mechanism of action | Common side effects |
|---|---|---|
| Thalidomide | Immunomodulatory | ■ Constipation<br>■ Arrhythmias<br>■ Venous thromboembolism<br>■ Peripheral neuropathy<br>■ Myelosuppression<br>■ Hypothyroidism<br>■ Somnolence |
| Lenalidomide | Immunomodulatory | ■ Myelosuppression particularly neutropenia<br>■ Venous thromboembolism<br>■ Arrhythmias<br>■ Constipation and less commonly diarrhoea secondary to bile acid malabsorption (Pawlyn et al, 2014)<br>■ Increased rates of secondary malignancies |
| Bortezomib | Proteasome inhibitor | ■ Myelosuppression particularly thrombocytopenia<br>■ Peripheral neuropathy<br>■ Gastrointestinal disturbance |
| Dexamethasone | Steroid | ■ Hypertension<br>■ Hyperglycaemia<br>■ Osteoporosis<br>■ Altered mood<br>■ Proximal myopathy<br>■ Thinning of skin leading to easy bruising |

## Supportive care treatments

As well as definitive treatment for multiple myeloma, patients also require treatments to help deal with the toxicities of chemotherapy and complications of the disease. Renal failure should be treated with steroids and intravenous fluids, and patients may need renal replacement therapy. In addition, hypercalcaemia and hyperuricaemia should be corrected and any nephrotoxic drugs such as non-steroidal anti-inflammatory drugs should be stopped. Infection, if present, should also be treated. Bortezomib-based regimens are ideal for patients presenting with renal failure or with a high light chain burden. Hyperviscosity is less common in multiple myeloma but can occur in IgG3 or IgA subtypes and requires urgent plasma exchange and definitive chemotherapy. Spinal cord compression is a medical emergency and requires discussion with both neurosurgical teams for potential surgical stabilization and also clinical oncology teams for urgent radiotherapy. High dose steroids are given immediately. Patients may also need input from orthopaedic teams for kyphoplasty, vertebroplasty and fixation of pathological fractures. Hypercalcaemia requires aggressive intravenous fluid replacement, steroid treatment and bisphosphonate therapy.

Patients on treatment or those with bone disease are given monthly bisphosphonate infusions (such as zolendronic acid) for bone protection. Patients with renal failure can be given pamidronate infusions at lower doses over longer infusion times. A well known side effect of bisphosphonates is osteonecrosis of the jaw. Patients should therefore routinely be referred to maxillofacial teams and any dental work completed if possible before commencing bisphosphonates.

Patients are also given prophylactic medications such as anti-emetics to prevent side effects of chemotherapy. Elderly, frail patients, those with serial infections or those given significantly immunosuppressive regimens are given prophylactic antibiotics to try to prevent infection. Aciclovir is given to patients on bortezomib-based regimens to prevent herpes simplex infections and shingles. The immunomodulatory drugs are associated with venous thromboembolism and so patients are given either aspirin or low molecular weight heparin prophylaxis depending on their risk of developing thrombosis while on treatment.

Many of the chemotherapy agents cause peripheral neuropathy (*Table 6*) and this can be treated with neuropathic agents such as pregabalin, amitryptiline or gabapentin. Patients may need referral to pain clinics or palliative care teams for symptom control. It is important to inform patients that they may develop significant fatigue. This is the result of a combination of disease, chemotherapy side effects and in particular steroid therapy.

## KEY POINTS

- Multiple myeloma is a common condition and should be considered in the differential in patients presenting with bony pain and haematological abnormalities.
- Key laboratory investigations include full blood count, renal function, calcium levels, albumin, serum/urine paraprotein and serum free light chain. Imaging should also be requested such as positron emission tomography-computed tomography, computed tomography or magnetic resonance imaging if available.
- A diagnosis of smouldering or asymptomatic multiple myeloma requires the absence of multiple myeloma defining events including high risk biomarkers and one or more lesions on magnetic resonance imaging.
- Patients should be treated in a multidisciplinary fashion and offered participation in clinical trials if possible.
- Standard of care in young fit patients includes combination chemotherapy with novel agents (thalidomide, bortezomib, lenalidomide) followed by autologous stem cell transplantation, while elderly patients are treated with chemotherapy alone.

**Table 7. New treatments for multiple myeloma**

| Drug | Mechanism of action | Advantages |
|---|---|---|
| Carfilzomib | Next generation proteasome inhibitor | ■ Minimal peripheral neuropathy<br>■ Safe in renal failure and elderly |
| Ixazomib | Next generation proteasome inhibitor | ■ Significant activity in relapsed refractory multiple myeloma<br>■ Oral therapy<br>■ Safe in patients with renal and hepatic impairment |
| Pomalidomide | Next generation immunomodulatory drug | ■ More potent than lenalidomide and thalidomide<br>■ Active in relapsed refractory multiple myeloma<br>■ Oral therapy |
| Elotuzumab | Immunostimulatory monoclonal antibody against SLAMF7 | ■ Active in relapsed refractory multiple myeloma<br>■ Works in synergy with lenalidomide and dexamethasone |
| Daratumumab | Anti-CD38 monoclonal antibody | ■ Active in relapsed refractory multiple myeloma<br>■ Currently in phase 3 clinical trials in combination with lenalidomide and dexamethasone |

All patients with multiple myeloma are at risk of infection and so should be given an annual flu vaccine. Patients with recurrent bacterial infections requiring admission to hospital and intravenous antibiotics may also be eligible for monthly low dose immunoglobulin infusions.

## New treatments and monoclonal antibody therapies in multiple myeloma

Several new drugs have been shown to be successful in the treatment of multiple myeloma. Although these are not yet routinely available, they are currently under evaluation by the European Medicines Agency or National Institute for Health and Care Excellence and may become available in the future. The mechanisms of action of these therapies are shown in *Table 7*.

Monoclonal antibody therapy is also a promising new treatment for multiple myeloma. CD38 is widely expressed by multiple myeloma cells and anti-CD38 antibody daratumumab has shown efficacy in phase I–II clinical trials (Lokhorst et al, 2015). Daratumumab induces cell death by complement-mediated and antibody-dependent cell-mediated cytotoxicity (De Weers et al, 2011). Further phase III clinical trials are currently in progress (POLLUX trial).

Elotuzumab also improved the overall response rate when used in combination with lenalidomide and dexamethasone compared to lenalidomide and dexamethasone alone in relapsed refractory multiple myeloma (ELOQUENT trial). Elotuzumab is an immunostimulatory monoclonal antibody that targets SLAMF7 (signalling lymphocytic activation molecule F7). SLAMF7 is a cell surface protein found on multiple myeloma cells and also on NK cells, thus causing selective killing of multiple myeloma cells as well as activation of NK cells (Lonial et al, 2015).

Other drugs currently in clinical trials include histone de-acetylase inhibitors, PI3Kinase inhibitors and chimeric antigen receptor therapies.

## Conclusions

Multiple myeloma is a common condition of the elderly and its incidence is increasing. Although this disease is generally incurable, a wide range of treatments is available and many new treatments are currently in clinical trials which may soon become available for routine use. This article highlights the new diagnostic criteria for asymptomatic multiple myeloma, the relevant investigations to confirm a diagnosis and discusses therapies currently in use for treatment. **BJHM**

*Conflict of interest: none.*


Berenson JR, Anderson KC, Audell RA et al (2010) Monoclonal gammopathy of undetermined significance: a consensus statement. *Br J Haematol* **150**(1): 28–38. https://doi.org/10.1111/j.1365-2141.2010.08207.x

Bird J, Behrens J, Westin J et al (2009) UK Myeloma forum and Nordic Myeloma study group: guidelines for investigation of newly diagnosed M proteins and the management of MGUS. *Br J Haematol* **147**: 22–42. https://doi.org/10.1111/j.1365-2141.2009.07807.x

Bird J, Owen RG, D'Sa S et al (2011) Guidelines for diagnosis and management of multiple myeloma. *Br J Haematol* **154**: 32–75. https://doi.org/10.1111/j.1365-2141.2011.08573.x

De Weers M, Tai YT, Van der Veer MS et al (2011) Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other haematological tumours. *J Immunol* **186**: 1840–1848. https://doi.org/10.4049/jimmunol.1003032

Dispenzieri A, Kyle RA, Katzmann JA et al (2008) Immunoglobulin free light chain ratio is an independent risk factor for progression of smouldering (asymptomatic) myeloma. *Blood*; **111**: 785–789. https://doi.org/10.1182/blood-2007-08-108357

Drayson M, Tang LX, Drew R et al (2001) Serum free light-chain measurements for identifying and monitoring patients with nonsecretory multiple myeloma. *Blood* **97**: 2900–2902. https://doi.org/10.1182/blood.V97.9.290

Kyle RA, Rajkumar SV (2009) Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. *Leukaemia* **23**: 3–9. https://doi.org/10.1038/leu.2008.291

Kyle RA, Therneau TM, Rajkumar V et al (2002) A long-term study of prognosis in monoclonal gammopathy of uncertain significance. *N Engl J Med* **346**: 564–569. https://doi.org/10.1056/NEJMoa01133202

Landgren O, Kyle RA, Pfeiffer RM et al (2009) Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. *Blood* **113**(22): 5412–5417. https://doi.org/10.1182/

blood-2008-12-194241
Lokhorst H, Plesner T, Laubach J et al (2015) Targeting CD38 with daratumumab monotherapy in multiple myeloma. *N Engl J Med* **373**: 1207–1219. https://doi.org/10.1056/NEJMoa1506348
Lonial S, Dimopoulos M, Palumbo A et al (2015) Elotuzumab therapy for relapsed or refractory multiple myeloma. *N Engl J Med* **373**: 621–631. https://doi.org/10.1056/NEJMoa1505654
Magrangeas F, Cormier ML, Descamps G et al (2004) Light-chain only multiple myeloma is due to the absence of functional (productive) rearrangement of the IgH gene at the DNA level. *Blood* **103**(10): 3869–3875. https://doi.org/10.1182/blood-2003-07-2501
Morgan GJ, Davies FE, Gregory WM et al (2013) Long-term follow-up of MRC Myeloma IX trial: Survival outcomes with bisphosphonate and thalidomide treatment. *Cancer Clin Res* **19**(21): 6030–6038. https://doi.org/10.1158/1078-0432
National Institute for Health and Care Excellence (2007) Bortezomib monotherapy for relapsed multiple myeloma. Guideline TA129. www.nice.org.uk/guidance/ta129 (accessed 11 January 2017)
National Institute for Health and Care Excellence (2009) Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy. Guideline TA171. www.nice.org.uk/guidance/ta171 (accessed 11 January 2017)
National Institute for Health and Care Excellence (2011) Bortezomib and thalidomide for the first line treatment of multiple myeloma. Guideline TA228. www.nice.org.uk/guidance/ta228 (accessed 11 January 2017)
National Institute for Health and Care Excellence (2014) Bortezomib for induction therapy in multiple myeloma before high dose chemotherapy and autologous stem cell transplantation. Guideline TA311. www.nice.org.uk/guidance/ta311 (accessed 11 January 2017)
Nau K, Lewis W (2008) Multiple myeloma: diagnosis and treatment. *Am Fam Physician* **78**(7): 853–859.
Palumbo A, Avet-Loiseau H, Oliva S et al (2015a) Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. *J Clin Oncol* **33**: 2863–2869. https://doi.org/10.1200/JCO.2015.61.2267)
Palumbo A, Bringhen S, Mateos M et al (2015b) Geriatric assessment predicts survival and toxicities in elderly myeloma: an International Myeloma Working Group report. *Blood* **125**(13): 2068–2074. https://doi.org/10.1182/blood-2014-12-615187
Pawlyn C, Khan MS, Muls A et al (2014) Lenalidomide-induced diarrhea in patients with myeloma is caused by bile acid malabsorption that responds to treatment. *Blood* **124**(15): 2467–2468. https://doi.org/10.1182/blood-2014-06-583302
Rajkumar SV, Kyle RA, Therneau TM et al (2005) Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. *Blood* **106**: 812–817. https://doi.org/10.1182/blood-2005-03-1038
Rajkumar SV, Lacy MQ, Kyle RA (2007) Monoclonal gammopathy of uncertain significance and smoldering multiple myeloma. *Blood Rev* **21**: 255–265. https://doi.org/10.1016/j.blre.2007.01.002
Rajkumar SV, Dimopoulous M, Palumbo A et al (2014) International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol* **15**: e538–e548. https://doi.org/10.1016/S1470-2045(14)70442-5
Raluy M, Ramagopalan S, Panjabi S, Lambrelli D (2014) Epidemiology and characteristics of patients with multiple myeloma in the UK. *Blood* **124**: 2048.
Regelink JC, Minnema MC, Terpos E et al (2013) Comparison of modern and conventional imaging techniques in establishing myeloma related bone disease: a systematic review. *Br J Haematol* **162**(1): 50–61. https://doi.org/10.1111/bjh.12346
Shephard E, Neal RD, Rose P et al (2015) Quantifying the risk of multiple myeloma from symptoms reported in primary care patients: a large case–control study using electronic records. *Br J Gen Pract* **65**(631): e106–e113. https://doi.org/10.3399/bjgp15X683545
Sonneveld P, Schmidt-Wolf IG, van der Holt B et al (2012) Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. *J Clin Oncol* **30**(24): 2946–2955. https://doi.org/10.1200/JCO.2011.39.6820
Wang Y, Yang F, Shen Y et al (2015) Maintenance therapy with immunomodulatory drugs in multiple myeloma: a meta-analysis and systematic review. *J Natl Cancer Inst* **108**(3): djv342. https://doi.org/10.1093/jnci/djv342