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Multiple myeloma

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Multiple myeloma is the second most common (10-15% of all) haematological cancer.[1] It is responsible for 15-20% of deaths from haematological cancer and about 2% of all deaths from cancer.[1] Recent improved understanding of the pathogenesis of myeloma has led to the development of new treatments. Although myeloma remains an incurable cancer, survival is improving, and newly diagnosed patients are now projected to live for around five years.[2] With an increasing number of survivors, it important for health professionals to understand the disease and current treatments. We have summarised guidelines, meta-analyses, and randomised controlled trials to give an up to date review of myeloma.

SOURCES AND SELECTION CRITERIA

We searched Medline and the Cochrane collaboration, using the terms "myeloma" and "multiple myeloma". Wherever possible, we used evidence from randomised controlled trials, systemic reviews, and meta-analyses, focusing mainly on articles published in the past five years, to provide an up to date summary. We have also referenced expert review articles and included opinion based on clinical experience.

What is myeloma and who gets it?

In myeloma, neoplastic plasma cells accumulate in the bone marrow (fig 1) and produce a monoclonal protein that is detected in the blood or urine (or both); this causes organ or tissue impairment. Epidemiological studies suggest that this is preceded by monoclonal gammopathy of undetermined significance (MGUS), an asymptomatic condition.[3] Myeloma generally affects older people (median age at diagnosis 70 years),[3] although the diagnosis should be considered at any age because 15% of cases are diagnosed under the age of 60 years and 2% under 40.[1 3] Myeloma is twice as common in Afro-Caribbeans as in white people, and in all racial groups incidence is 50% higher in men than in women.[4] There are no known hereditary genetic components or definite environmental risk factors.[5]

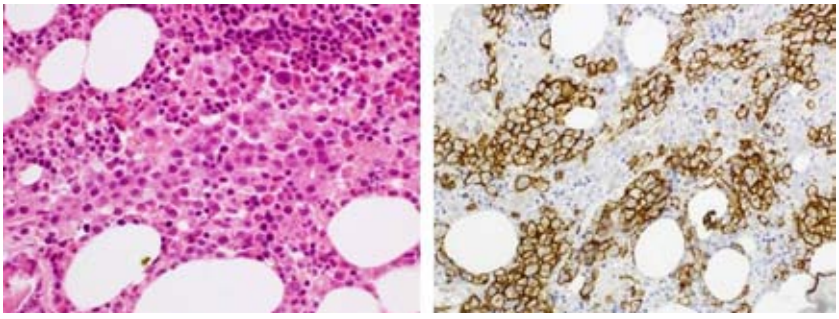

Fig 1| Bone marrow trephine biopsy from a patient with multiple myeloma showing a heavy infiltrate of plasma cells. Haemotoxylin and eosin staining (left) and immunohistochemical staining using anti-CD138 antibody (right) highlight the plasma cells

SUMMARY POINTS

In the past decade, the use of immunomodulatory drugs and proteasome inhibitors has improved the outlook for patients with myeloma, but myeloma remains an incurable cancer

Triple drug combinations are now standard induction regimens, followed by autologous stem cell transplantation in patients who are young and fit enough

Early aggressive management of patients presenting in renal failure is vital to preserve renal function

Treatment paradigms for spinal disease are changing, with radiotherapy and vertebral augmentation sometimes preferred over surgery

Bone morbidity, organ failure, and side effects of treatment contribute to a high burden of disease, and early engagement with palliative care and symptom control teams is vital to optimise treatment outcomes and quality of life

What is the underlying pathophysiology?

Myeloma arises because of genetic changes that occur during the terminal differentiation of B lymphocytes into plasma cells. In around half of cases, a chromosomal translocation occurs, which places an oncogene into the immunoglobulin heavy chain gene on chromosome 14 (IgH translocation). This results in overexpression of the oncogene and dysregulated cell proliferation. The remaining cases are characterised by trisomies of several odd numbered chromosomes—that is, chromosomes 3, 5, 7, 9, 11, 15, 19, and 21. The presence of these numerous trisomies is called hyperdiploidy. As myeloma develops, further genetic events, such as *RAS* mutations, occur.[6] Because the growth and survival of myeloma cells is dependent on other cells in the bone marrow—such as fibroblasts, osteoblasts, osteoclasts, stromal cells, and dendritic cells—treatments that target the bone marrow environment have been developed.[7]

What causes bone disease and hypercalcaemia in myeloma?

Imbalanced bone remodelling in the myeloma bone marrow is caused by increased osteoclast activity, together with reduced osteoblast function. Myeloma cells cause an increased production of osteoclast activating factors and cytokines that inhibit osteoblast differentiation. The unopposed osteolysis is also responsible for hypercalcaemia.

What causes renal impairment?

In most cases malignant plasma cells produce a paraprotein—a monoclonal immunoglobulin—typically IgG or IgA. IgM paraproteins are not usually found in myeloma, and their presence suggests an alternative diagnosis, such as Waldenström's macroglobulinaemia. Plasma cells also produce varying amounts of monoclonal free light chains. Light chains in the urine, referred to as Bence Jones proteins, are found in myeloma and MGUS. Around 20% of patients with myeloma produce only light

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chains in the serum and urine, whereas 2% produce neither light chains nor a paraprotein and are termed non-secretors. Light chains are filtered in the glomeruli and reabsorbed in the proximal tubules. When the light chain load exceeds this reabsorptive capacity, light chains precipitate out as casts in the distal tubule, causing tubular obstruction and tubulo-interstitial inflammation, and lead to acute kidney injury. Cast nephropathy causes 90% of renal impairment in myeloma. Other causes include amyloid deposition, dehydration, hypercalcaemia, hyperviscosity, and nephrotoxic drugs, such as non-steroidal anti-inflammatory drugs.[8]

How does myeloma present?

Common presentations are symptoms of anaemia (seen in 75% of patients at diagnosis), hypercalcaemia (30%), renal impairment (25%), and bone disease (70%).[3 9 10] Bone manifestations can present as painful lytic lesions, vertebral crush fractures, or long bone fractures (fig 2). Spinal cord compression due to retropulsion of pathological vertebral fractures or extramedullary soft tissue plasmacytomas occurs in 5% of patients with myeloma.[3] Hypercalcaemia, acute renal failure, and cord compression are medical emergencies, and prompt diagnosis and treatment are vital to minimise long term organ damage. High paraprotein values can cause symptoms of hyperviscosity (headaches, epistaxis, blurred vision, and confusion), while decreased humoral immunity results in recurrent bacterial infections. Thirty per cent of cases are diagnosed after an incidental finding of raised erythrocyte sedimentation rate, total protein, or immunoglobulins.

Presenting symptoms are often non-specific—for example, lethargy or back pain—and this can delay the diagnosis. In one recent report, 56% of patients presenting to general practice waited more than six months to see a haematologist.[11] A third of cases are diagnosed through the emergency route, rather than general practice referrals, and these patients have a worse prognosis (51% *v* 82% one year survival).[12]

How is myeloma diagnosed?

Box 1 summarises the International Myeloma Working Group diagnostic criteria for myeloma, asymptomatic myeloma, and MGUS.[13] MGUS is diagnosed when plasma cell infiltration and paraprotein concentrations are low and the patient has no evidence of myeloma, such as hypercalcaemia, renal insufficiency, anaemia, or bone lesions. Patients with MGUS have around a 1% chance each year of progressing to myeloma.[14] When plasma cell or monoclonal protein concentrations are higher but there is no myeloma related organ or tissue impairment, the condition is referred to as asymptomatic myeloma. This condition carries a 10% chance each year of progression to symptomatic myeloma.[3] A polyclonal rise in immunoglobulins reflects an acute inflammatory response and not MGUS or myeloma. Box 2 summarises the investigations to perform when a diagnosis of myeloma is being considered, highlighting screening tests for general practitioners. Clinical suspicion of myeloma, combined with one or more of anaemia, impaired renal function, hypercalcaemia, lytic lesions on radiography, or detection of a paraprotein or urinary Bence Jones proteins warrants referral to a haematology clinic.

A skeletal survey using plain radiographs of the spine, skull, chest, pelvis, and the upper bones of the limbs is needed to determine the extent of myeloma bone disease.[15] Magnetic resonance imaging is the gold standard imaging modality to investigate vertebral disease and

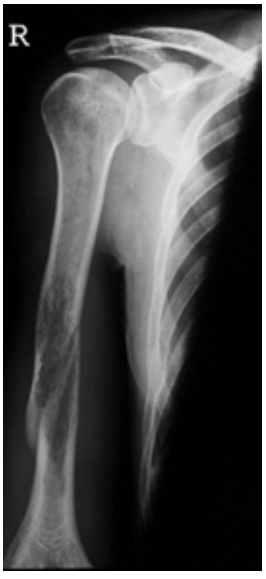

Fig 2| Plain radiograph showing spiral fracture through right humerus. This patient had previously been fit and well but presented with fracture of his right arm

Box 1 | International Myeloma Working Group diagnostic criteria[13]

Symptomatic myeloma
All three criteria needed for diagnosis:
Monoclonal plasma cells in marrow ≥10%
Monoclonal protein in serum or urine (unless non-secretory; if so, need ≥30% monoclonal plasma cells in bone marrow)
Evidence of myeloma related organ or tissue impairment:
- Hypercalcaemia (>10.5 mg/dL (2.6 mmol/L) or upper limit of normal)
- Renal insufficiency (serum creatinine >2 mg/dL (176.8 µmol/L)
- Anaemia: haemoglobin <100 g/L or 20 g below normal range
- Lytic bone lesions, osteoporosis, or pathological fractures

Asymptomatic myeloma
Both criteria needed for diagnosis:
Monoclonal protein ≥30 g/L or monoclonal plasma cells in marrow ≥10%
Absence of myeloma related organ or tissue impairment

MGUS
All three criteria needed for diagnosis:
Monoclonal protein <30 g/L
Monoclonal plasma cells in bone marrow <10%
Absence of myeloma related organ or tissue impairment

Box 2 | Investigations for diagnosing myeloma[3]

Screening tests
To be performed by general practitioner if clinical suspicion of myeloma:
Full blood count
Serum urea and creatinine
Erythrocyte sedimentation rate or plasma viscosity
Serum calcium and albumin measurement
Immunoglobulins and serum electrophoresis
Measurement of urinary Bence Jones protein
Radiography of symptomatic areas

Tests to establish the diagnosis
To be performed by a haematologist:
Bone marrow aspirate and trephine, with plasma cell phenotyping
Immunofixation of serum and urine
Measurement of serum free light chains
Skeletal survey

Tests to estimate tumour burden and prognosis
To be performed by a haematologist:
Fluorescence in situ hybridisation analysis of bone marrow aspirate
Serum β_2 microglobulin concentration
Serum albumin concentration
Quantification of monoclonal proteins in serum and urine

Box 3 | International staging system[16]

Stage I

Serum β_2 microglobulin <3.5 mg/L and albumin ≥35 g/L

Stage II

Does not fit criteria for stage I or II

Stage III

Serum β_2 microglobulin ≥5.5 mg/L (regardless of albumin level)

possible spinal cord compression. If it is unavailable, computed tomography should be performed. Nuclear medicine bone scintigraphy has no role in myeloma because skeletal uptake of technetium relies on the osteoblastic reaction, which is reduced or absent. Thus myeloma lytic lesions are typically "cold" on a bone scan. Positron emission tomography-computed tomography may have a role in screening for, and monitoring, extramedullary sites of disease, especially in non-secretory myeloma.[15]

What are the prognostic factors?

Although the introduction of novel therapeutic agents has transformed the outlook for many patients, myeloma remains a heterogeneous disease. Some patients will live for more than eight years after diagnosis, whereas a subset with high risk disease will die within 24 months.[2] The international staging system defines three risk categories based on serum concentrations of β_2 microglobulin and albumin (box 3).[16] Specific genetic lesions, or gene signatures, are associated with worse outcomes.[2] IgH translocations involving chromosomes 4 and 16, termed t(4;14) and t(14;16) are considered high risk and are associated with a worse prognosis. The tumour suppressor gene *P53* is located on the short arm, or p arm, of chromosome 17, and deletion of this arm (del 17p) is also associated with a worse outcome. Patients with the t(11;14) or t(6;14) IgH translocations are considered to have standard risk disease, as are patients with hyperdiploidy.

Age is an independent prognostic factor, as is response to treatment.[17] Achievement of a complete response is associated with prolonged progression-free survival and overall survival. Younger patients who are fit enough for high dose chemotherapy now have a projected median survival of around seven years.[18] Patients who present through the emergency route have a worse prognosis,[12] and a small retrospective case review study showed a trend towards reduced overall survival in patients with a delay in diagnosis greater than six months.[11]

How is myeloma treated?

Patients with MGUS and asymptomatic myeloma are observed but not treated until they develop symptomatic myeloma. No intervention has been found to delay or prevent the progression of MGUS to myeloma.[3 14] Patients with asymptomatic myeloma should be followed up under the supervision of a consultant haematologist. Randomised controlled trials found that treating asymptomatic myeloma with chemotherapy had no impact on survival.[3] Current trials are investigating the use of novel agents to treat those at high risk of progression to symptomatic myeloma, and patients should be offered entry into these if available.[3] British Committee for Standards in Haematology (BCSH) guidelines recommend monitoring patients with MGUS who are at low risk of progression to

Drugs commonly used in the treatment of myeloma

Name	Class of drug	Uses	Treatment route
Thalidomide	Immunomodulatory agent	In combination with dexamethasone, ±cyclophosphamide, both frontline and at relapse	Oral
Bortezomib	Proteasome inhibitor	With dexamethasone ±cyclophosphamide or thalidomide at relapse; frontline in renal failure and in combination with melphalan and prednisolone in patients who are ineligible for a transplant	Subcutaneous, intravenous
Lenalidomide	Immunomodulatory agent	With dexamethasone at relapse	Oral
Dexamethasone	Steroid	In combination with most antimyeloma agents, both at relapse and frontline	Oral
Melphalan	Alkylating agent	High dose intravenous melphalan is used for conditioning before autologous stem cell transplantation; oral melphalan is used frontline with prednisolone and bortezomib or thalidomide in patients who are ineligible for a transplant	Oral, intravenous
Cyclophosphamide	Alkylating agent	In combination (oral) with dexamethasone and thalidomide or bortezomib, relapse or frontline; single agent (intravenous) as part of mobilising regimen	Oral, intravenous
Doxorubicin	Anthracycline	In combination with bortezomib and dexamethasone, both frontline and at relapse	Intravenous
Bendamustine	Alkylating agent	In combination with thalidomide and prednisolone or dexamethasone, at relapse	Intravenous
Carfilzomib	Next generation proteasome inhibitor	Current use limited to clinical trials	Intravenous
Pomalidomide	Next generation immunomodulatory agent	Current use limited to clinical trials	Oral

Box 4 | Classifying disease response or progression in myeloma[42]

This is traditionally done on the basis of the size of reduction (or rise) in paraproteins, but the degree of plasmacytosis in the bone marrow, progression of bone lesions, and the existence of soft tissue plasmacytomas are also taken into account. As techniques for detecting residual myeloma cells in the bone marrow advance, new depths of response are being acknowledged, such as stringent complete response

Complete response

No detectable paraprotein and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow

Very good partial response

Greater than 90% reduction in paraproteins or paraproteins detectable but too low to measure

Partial response

Greater than 50% reduction in paraproteins

No change or stable disease

Not meeting criteria for disease response or progression

Progressive disease

At least a 25% increase in paraproteins (increase of at least 5 g/L), development of new bone lesions or plasmacytomas, or hypercalcaemia (corrected serum calcium >2.65 mmol/L)

myeloma in primary care, whereas those at high risk of progression should be monitored under supervision of a consultant haematologist. Fig 3 (on bmj.com) shows an algorithm for the management of a newly detected paraprotein, including frequency of follow-up for patients with MGUS in primary care and triggers for referral to haematology.

The past decade has seen an unprecedented advance in the treatment of symptomatic myeloma, with the introduction of bortezomib (a proteasome inhibitor) and thalidomide and lenalidomide (immunomodulatory drugs) (table). These agents are now the mainstay of treatment. Most patients respond to initial treatment and enter a period of disease stability,[17 19-22] which is generally associated with good quality of life. Because of the lack of curative treatment, relapse is inevitable, but at least half of patients respond to chemotherapy a second time, using similar or different drugs. Subsequent relapses become increasingly less responsive to treatment, until refractory end stage disease ensues, sometimes with extramedullary manifestations and cytopenias (fig 4, bmj.com). At most stages of treatment clinical trials are available and should be offered to patients if they are eligible.

The approach to treating newly diagnosed symptomatic myeloma depends on age and comorbidities. Initial chemotherapy regimens aim to achieve the deepest response with the lowest toxicity, and for patients who are young (generally <65 years) and fit enough, this is consolidated with high dose chemotherapy with autologous stem cell transplantation. Older patients, or those with serious comorbidity, who are not fit enough to undergo autologous transplantation are treated with chemotherapy only. Response to treatment is graded according to the reduction in paraproteins or light chains (box 4). Box 5 lists the major side effects of treatments.

Box 5 | Main side effects of drugs used to treat myeloma

Corticosteroids
Gastrointestinal side effects
Hyperglycaemia
Immunosuppression
Insomnia and altered mood

Alkylating agents (cyclophosphamide, melphalan)
Nausea

Myelosuppression

High dose melphalan
Mucositis
Gastrointestinal toxicity
Alopecia

Thalidomide†
Constipation
Somnolence
Sensorimotor peripheral neuropathy*
Autonomic neuropathy (less common)*
Bradycardia, altered thyroid function
Increased thrombotic risk

Bortezomib
Sensory neuropathy—can be painful*
Autonomic neuropathy—postural hypotension, altered bowel habit*
Thrombocytopenia
Reactivation of varicella zoster virus

Lenalidomide†
Constipation
Fatigue
Myelosuppression
Increased risk of thrombosis

*Symptoms must be monitored vigilantly—the dose may need to be reduced or the schedule changed.

†Because this drug has teratogenic effects, conditions of a pregnancy prevention programme must be fulfilled for all male and female patients before the drug is prescribed.

Treatment of patients eligible for transplantation

Several large phase III trials have established the use of high dose chemotherapy and autologous stem cell transplantation as standard of care in patients deemed young and fit enough.[23] Initial induction therapy should preserve haemopoietic stem cell function so that stem cells can be collected. The traditional vincristine-doxorubicin-dexamethasone regimen has been superseded by new agents. Several randomised studies have shown that induction regimens incorporating one or more novel agent induce higher disease responses before and after autologous stem cell transplantation and extend progression-free survival.[17 19 20 22] The best evidence exists for regimens that contain bortezomib, which are used with dexamethasone and usually a third agent—thalidomide, doxorubicin, or cyclophosphamide.[24 25] The thalidomide based regimen, cyclophosphamide-thalidomide-dexamethasone, is widely used in the United Kingdom, as a result of the recent Myeloma IX study. This practice may change, however, when the results of the current national studies—Myeloma XI and PADIMAC—are released. Myeloma XI is investigating a lenalidomide combination, whereas PADIMAC is using a bortezomib based induction protocol.

The use of tandem (or double) autologous stem cell transplantation to deepen the response and extend progression-free survival has been explored in randomised controlled trials, and benefit seems to be restricted to patients who do not respond well to the first transplant.[26 27] Allogeneic stem cell transplantation has curative potential, but high transplant related mortality, and a meta-analysis shows no survival advantage over autologous stem cell transplantation. This approach should be considered only in the context of a clinical trial.[28]

What are the treatment options in patients unsuitable for transplantation?

The combination of melphalan and prednisolone has been a mainstay of treatment in older patients since the 1960s. This has changed with the outcome of several randomised trials comparing this combination with the combination plus a novel agent, either thalidomide or bortezomib.[13] A meta-analysis of six trials concluded that the addition of thalidomide improved progression-free survival by 5.4 months and overall survival by 6.6 months.[13] The addition of bortezomib improved the response rate, time to progression, and increased overall survival by 13 months.[21] Melphalan and prednisolone plus thalidomide or bortezomib

is therefore considered the standard of care for patients ineligible for transplantation.[13] The cyclophosphamide-thalidomide-dexamethasone regimen used in the Myeloma IX trial produced higher response rates than melphalan and prednisolone, but progression-free survival and overall survival were similar for both regimens.[29]

How is relapse treated?

Management of relapse depends on previous treatment, length of remission, and persisting toxicities and comorbidities. Generally, the previous treatment is used again only if it had resulted in a long progression-free survival (12 months or more). Novel agents are the mainstay of treatment at relapse and are more efficacious if combined with corticosteroids, and sometimes an alkylating agent.[3] In general, first relapse is treated with a bortezomib regimen, whereas lenalidomide is used for subsequent relapse, in accordance with National Institute for Health and Care Excellence recommendations in England and Wales. A second autologous stem cell transplant may be considered in patients who are young and fit enough and who achieved a long (≥18 months) remission after first transplant.

The outlook for patients who do not respond to immunomodulatory agents and bortezomib is poor, with a median overall survival of nine months.[30] This highlights the importance of entering these patients into clinical trials, to allow access to newer treatments and evaluate their efficacy.

How should myeloma presenting with acute kidney injury be managed?

A linear association has been reported between a reduction in free light chains in the serum and renal recovery; this emphasises the importance of starting chemotherapy promptly or directly removing light chains, through plasmapheresis or haemodialysis.[31]

Randomised controlled trials and retrospective studies have shown that bortezomib has rapid anti-myeloma activity and is safe in renal impairment.[32 33] An International Myeloma Working Group consensus statement recommends bortezomib plus high dose dexamethasone as the treatment of choice for patients presenting with renal failure.[33] A recent single centre study in newly diagnosed patients reported that both bortezomib and thalidomide based regimens were effective in reversing renal failure.[32] The addition of plasmapheresis to conventional chemotherapy did not improve outcomes in a recent randomised study,[34] but high cut-off haemodialysis with a new generation of protein permeable dialysers to remove free light chains is now being studied.[35]

How should vertebral disease be managed?

If cord compression is suspected, dexamethasone should be started immediately,[3] followed by urgent imaging of the spine. Bone related cord compression requires urgent discussion with neurosurgical and orthopaedic teams to consider decompression or stabilisation of the spine. Where cord compression is caused by extramedullary tumour, chemotherapy or radiotherapy (or both) may be preferable.

Vertebral augmentation involves the percutaneous injection of polymethylmethacrylate into vertebral compression fractures, and the consensus among experts is that it reduces pain more rapidly than radiotherapy.[36] There are two techniques, vertebroplasty and balloon kyphoplasty, during which a balloon is inflated in the fractured vertebra before injection. Vertebroplasty can be effective in reducing pain.[37] International Myeloma Working Group guidelines state that vertebral augmentation should be the procedure of choice for painful compression fractures. Pain due to disease, but with no fracture, should be treated with radiotherapy.[36]

How is hyperviscosity treated?

Symptoms of hyperviscosity are caused by high concentrations of paraprotein (IgA >40 g/L, IgG >60 g/L).[3] If symptomatic, urgent plasma exchange should be performed and systemic antimyeloma treatment started. If plasmapheresis is unavailable, isovolaemic venesection may be beneficial.

How is bone disease managed?

Bisphosphonates are the mainstay of treatment for myeloma bone disease and three are licensed for use in myeloma: sodium clodronate, pamidronate, and zoledronic acid. A meta-analysis of 16 randomised controlled trials found that, compared with placebo, bisphosphonates significantly reduced vertebral fractures, skeletal related events, and bony pain. Results from the Myeloma IX trial indicate that zoledronic acid is superior to clodronate in reducing skeletal related events, with a benefit also for overall survival.[10] Bisphosphonates are recommended for all patients with symptomatic myeloma, regardless of bone lesions,[3] and zoledronic acid is the preferred agent, but should be used with caution in renal failure.[10] Most

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals

International Myeloma Foundation (http://myeloma.org)
—Includes International Myeloma Working Group guidelines, along with details of clinical trials and research

British Committee for Standards in Haematology (www.bcshguidelines.com)
—Up to date evidence based guidelines on the diagnosis and treatment of myeloma, supportive care in myeloma, and the management of monoclonal gammopathy of undetermined significance

UK Myeloma Forum (www.ukmf.org.uk)
—Aims to develop guidelines, encourage collaborative research, provide advocacy, and promote education within myeloma

TAKE 2 (www.myeloma.org.uk/get-involved/awareness-and-campaigns/the-take-2-campaign)
—Awareness campaign run by Myeloma UK; provides general practitioners with a myeloma diagnosis pathway to aid early diagnosis

Resources for patients

Myeloma UK (www.myeloma.org.uk)
—Registered charity that deals exclusively with myeloma; provides patient support and education

Macmillan Cancer Support (www.macmillan.org.uk)
—Provides practical, medical, and financial support to people diagnosed with cancer

guidelines recommend at least two years of treatment. Bisphosphonates are associated with an increased risk of osteonecrosis of the jaw, and a dental assessment is recommended before starting treatment.[3]

What supportive care measures are important?

Pain control is often a major aspect of clinical care, owing to bone disease or side effects of treatment. Radiotherapy can effectively treat painful skeletal lesions, as well as soft tissue disease. Vertebral augmentation and bisphosphonates may be beneficial. Opiates are often needed to manage bone pain. Avoid non-steroidal anti-inflammatory drugs because of potentially serious renal toxicity.[9] For neuropathic pain, calcium channel blockers (such as gabapentin) or serotonin noradrenaline reuptake inhibitors (such as amitriptyline) may help.[9] Early engagement with the multidisciplinary team is important, for symptom control and psychosocial support.

Myeloma is associated with an increased risk of venous thromboembolism, which is further increased by immunomodulatory agents, particularly when combined with corticosteroids or cytotoxic agents and in newly diagnosed patients.[9] BCSH guidelines recommend that patients starting immunomodulatory treatment should receive aspirin or low molecular weight heparin, according to risk.[9]

Anaemia can be managed with transfusions or erythropoietic stimulatory agents. BCSH guidelines suggest a trial of such agents if haemoglobin is <100 g/L.[9] Myeloma and its treatment lower immunity, and 10% of patients die, largely of infection, within the first 60 days. Patient education and 24 hour access to haematology advice are important preventive measures, as is prompt initiation of antibiotics.

What new treatments can we expect?

Despite high rates of response to initial treatment, most patients relapse within 36 months, so the use of consolidation or maintenance treatment to prolong progression-free survival has been studied intensively. Consolidation involves a limited duration of treatment aimed at deepening disease response, whereas maintenance is extended treatment (until relapse) to maintain disease response. Studies of maintenance with thalidomide or lenalidomide have shown some benefit, but longer follow-up is needed.[38] The use of pre-emptive treatment in patients with asymptomatic myeloma who have high risk features is also being studied.[17] Clinical trials are evaluating new treatments, new combinations of existing treatments, and different sequencing and durations of treatment. Pomalidomide, a next generation immunomodulatory agent, and carfilzomib, a proteasome inhibitor (table) have been approved by the US Food and Drug Administration. Antibodies against surface antigens such as CD38 and CS1 have also shown early promise.[39 40] Disease heterogeneity continues to be a challenge, and risk stratified approaches are being increasingly explored. With increased understanding of the pathophysiology of myeloma bone disease, bone anabolic approaches and antiresorptive treatments are being studied.[41]

TIPS FOR NON-SPECIALISTS

- Consider a diagnosis of myeloma in patients with bone pain, unexplained anaemia, recurrent infections, fatigue, or renal failure
- Myeloma can occur in people under 60 years of age, including very young adults
- Spinal cord compression, hypercalcaemia, and acute renal failure secondary to myeloma are medical emergencies and should be discussed with a haematologist immediately
- Patients with myeloma often have diminished renal reserve, and care should be taken when prescribing antibiotics or other potentially nephrotoxic drugs

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ANSWERS TO ENDGAMES, p 40

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STATISTICAL QUESTION

Meta-analyses: heterogeneity and subgroup analysis

Statements *b* and *d* are true, whereas *a* and *c* are false.

PICTURE QUIZ **Erythroderma in the emergency department**

1 Toxic erythema, an adverse drug eruption, HIV seroconversion, secondary syphilis, pityriasis rubra pilaris, acute eczema or psoriasis, or cutaneous T cell lymphoma.

2 Dermatological review; skin biopsy and admission; stop possible causative drugs; monitor fluid balance, pulse, blood pressure, and temperature; and frequent application of greasy emollients.

3 Blood tests (full blood count; urea and electrolytes; liver function tests; C reactive protein; erythrocyte sedimentation rate; IgE titre; serology for HIV, cytomegalovirus, Epstein-Barr virus, rubella, parvovirus, and mycoplasma; and blood cultures) plus skin biopsy help identify the cause of this patient's erythroderma (box 1).

4 By taking a comprehensive history of temporal associations between prescribed and over-the-counter drugs and the onset of rash.

5 Drug hypersensitivity syndrome can be diagnosed by identification of at least three of the seven diagnostic criteria defined by the European registry of severe cutaneous adverse reactions to drugs and collection of biological samples.