

Management of Multiple Myeloma

Introduction

Multiple myeloma (MM) is a disorder in which malignant plasma cells accumulate usually in the bone marrow. There, intricate interactions occur between the bone marrow microenvironment and the myeloma cells, causing bone destruction which in turn stimulates tumour growth. These terminally differentiated B lymphocytes all produce (and usually secrete) in individual patients a unique serum 'monoclonal' immunoglobulin (Ig), usually IgG or IgA, and/or sometimes a restricted light chain in the urine (Bence-Jones).

Myeloma accounts for around 1% of all cancer-related deaths in Western countries and constitutes 10% to 15% of haematological malignancies. In 1990, the annual age-standardised incidence in England and Wales was 5.1 and 3.5 per 100,000 for men and women respectively. The annual incidence of MM in South East England (with the population of about 14 million) has not varied during the decade 1990 to 1999, ranging between 3.8 and 4.5 per 100,000.

Specifically, in 1999 for selected ages 60-64 years, the incidence is 11.4 per 100,000 and for 80-84 years is 45.1 per 100,000 ([Thames Cancer Registry](#)). With a rapidly increasing proportion of the population surviving over 70 years, an increase in overall incidences is inevitable. Males are slightly more commonly affected than females, and blacks have nearly twice the incidence of whites.

Up until the early 1980s, MM caused a slow progressive decline in quality of life until death came after about 2 years. This changed in the early 1980s following the observation that a single high dose of an alkylating agent (melphalan) could produce a clinical state in which by ordinary macroscopic means, the disease had disappeared i.e. a state of complete remission (CR), and the thinking thereafter for treatment strategies of myeloma has followed those pioneered two decades earlier for leukaemia. Now, patients have doubled their survival and spend most of their myeloma lifetime with a normal quality of life. 30% can expect to live longer than 10 to 20 years and for the longer survivors, a significant number are living a normal life span for their age, which has led to the term 'operational cure'.

Learning Objectives

The activities and content of this module are built around the following learning objectives:

- To understand the distinguishing features between MM and monoclonal gammopathy of unknown significance (MGUS), solitary plasmacytoma, smouldering myeloma and plasma cell leukaemia
- To diagnose and manage the medical emergencies relating to MM in an efficient manner.
- To gain an understanding of the treatment strategy for MM including high-dose therapy.
- To gain an awareness of the different novel drugs available to patients today and explore the different treatment decisions that a patient can make.

This module is designed to give a broad overview of MM and to lead the reader to more detailed texts to gain greater understanding. It aims to show the reader how decisions are made in MM management with the use of activities, examples and a discussion forum.

Diagnosis of Multiple Myeloma (MM)

An increasing proportion of patients with MM are diagnosed by chance in the absence of any symptoms, usually when screening laboratory studies reveal a raised total protein or high ESR. Also, patients with MM are now being diagnosed earlier than in the past due to greater awareness of the disease. Patients with MM usually present with infections, bone symptoms or renal failure and are found to have one or more of a triad consisting of a monoclonal paraprotein (in the serum or urine), bone lesions and bone marrow infiltration with malignant plasma cells. These and other laboratory investigations to help in diagnosing MM and its complications are listed in [Table 1](#). Occasionally, the malignant clone of plasma cells proliferates as an isolated tumour in the soft tissues and is termed solitary plasmacytoma which may progress to MM. Also, plasma cells can proliferate as a pre-myelomatous condition, detectable perhaps for years only as an isolated finding of a monoclonal paraprotein in the serum termed Monoclonal gammopathy of undetermined significance (MGUS). Not all MGUS patients transform to MM.

Smouldering myeloma is a loose term which is a half-way house between MGUS and florid MM. The differentiating features between these entities are described in [Table 2](#).

Another rare variant of MM is plasma cell leukaemia which is defined as an absolute plasma cell count of more than $20 \times 10^9/L$, with plasma cells also comprising more than 20% of the total leukocyte count. This may present primarily or develop secondarily in patients with MM undergoing treatment. Treatment is similar to patients with MM.

Patients with smouldering MM and Stage IA MM may not require treatment if they are asymptomatic, hence it is essential to get the accurate staging.

Protein chemistry

Protein chemistry forms the basis of diagnosing MM in majority of patients. The malignant cell in MM produces a unique protein (immunoglobulin or light chain) which is usually secreted into the serum (or urine). This monoclonal paraprotein (M protein) is the most widely accepted and used marker to assess disease response and monitor the course of disease in the individual patient. Although the quantity of paraprotein has been used to distinguish between MGUS and MM or between stage I and III myeloma, it is not a reliable parameter, because there is not a link between the amount of paraprotein and the likelihood of destructive bone disease i.e. many stage III myeloma patients may have a paraprotein that is less than 30 g/L. Until recently, the standard protein assessment of MM consisted of using agarose gel (or cellulose acetate) electrophoresis but now this has been replaced by the more reproducible and faster capillary zone electrophoreses. The heavy chain (IgG, A, D or E) and light chain isotypes (kappa or lambda) are identified using IEP or IF. 24-hour urine light chain assays monitor disease progress. IgG occurs in 53% of patients, IgA in 25%, IgD in 1%, and 20% of patients will have only light chains (light-chain myeloma). Non-secretory myeloma occurs in 1% patients. See [Table 3](#) for protein markers.

Activity 1 (allow 60 minutes)

Task 1: A patient has presented with serum paraprotein found on a routine blood test. Would you treat?

Allow 30 minutes

- Perform a PubMed search on MGUS
- Read a review article on the management of MGUS

Task 2: Review national and international guidelines on MGUS

Allow 30 minutes

Thinking Point:

- Would you treat an asymptomatic patient with an incidental finding of paraprotein with all other blood tests being normal?
- How would you follow them up?
- At what stage would you consider treatment?

Resources required to complete this activity

Useful websites

Pubmed

www.pubmedcentral.nih.gov

The National Comprehensive Cancer Network (NCCN)

www.nccn.org

The British Committee for Standards in Haematology (BCSH)

www.bcsguidelines.com

Background reading

Kyle RA, Rajkumar SV. (2007) Monoclonal gammopathy of undetermined significance and smoldering multiple myeloma. *Hematology Oncology Clinics of North America*. 21(6): 1093-1113, ix.

Durie BGM, Salmon SE. (1975) A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. *Cancer*. 36: 842-854.

Greipp PR, San Miguel J, Durie BG et al. (2005) International staging system for multiple myeloma. *Journal of Clinical Oncology*. 23(15): 3412-3420.

Staging of Multiple Myeloma

In 1975, Durie and Salmon devised a staging system which is still followed by many centres using haemoglobin, paraprotein level, renal and bone disease. This worked well 25 years ago when patients did not have many treatment choices but with modern treatment producing CRs, those prognostic factors are no longer valid. New staging systems have so far depended on single-centre studies showing age, β 2M, deletion13, labelling index, immunologic subtype of myeloma, albumin, and several other factors having roles to play but no coordinated multi-centre group using modern treatment has optimised these factors in a multivariate analysis of independent variables.

The International staging system (ISS) is currently the most accepted one and is followed by all major centres. Serum free light chain assay is currently being standardized and hopefully in the future will be part of the staging systems. The following link to the [American Cancer Society](#) website describes both current ISS system with the Durie-Salmon staging system.

Presenting symptoms and treatment during first 24 hours

Although the symptoms of a MM patient may have often been present for months, the moment at which the diagnosis becomes apparent is often dramatic unless the patient has had a routine blood test which shows a high serum protein level. The first 24 hours during which the diagnosis is made may be critical. Patients may present with the following symptoms:

Sepsis

25% of patients with MM present with infection, commonly as a spectrum of problems ranging from general debility with fever through to overwhelming sepsis. Shingles is also common. Sometimes the patient is not pyrexial because of profound immunoparesis which inhibits host responses. It is therefore essential that all new patients with MM who are non-specifically ill are admitted, hydrated and given broad spectrum intravenous antibiotics after blood cultures have been taken, and before all routine investigations have been completed. Hours may be critical in this context. Fungal infections at diagnosis are rare, as is meningitis.

Renal failure

Renal failure occurs in nearly 25% of MM patients at presentation. It is usually multifactorial involving sepsis, hypercalcaemia, dehydration, hyperviscosity, amyloid, and more rarely hyperuricaemia and infiltration of the kidney by myeloma cells. Tubular damage associated with the excretion of light chains is almost always present⁴¹. Treatment depends on identifying precipitating causes, but also the priority must be to give specific myeloma treatment as quickly as possible even if this involves renal support using plasma-exchange, haemofiltration or dialysis. In about half of the patients presenting with renal impairment, it is reversible with good renal support therapy including early institution of definitive chemotherapy.

Hyperviscosity

Approximately, 80% of patients can present with anaemia, and care needs to be taken in transfusing these patients especially if they have hyperviscosity syndrome which is seen commonly in patients with IgM myeloma. Plasma exchange using blood cell separators in conjunction with red cell exchange can be used to bring patients who are in heart failure with severe anaemia into a normalised haemodynamic state within a few hours. Patients with bleeding at presentation with or without thrombocytopenia need urgent plasmaphereses if hyperviscosity is present. These patients are at grave risk of cerebral and retinal damage if left untreated. Erythropoietin, known to be of benefit to patients with hemoglobin <12g/dL at later stages of the disease, may also be useful at the beginning to reduce transfusion requirements during the initial period.

Bone pain / pathological fractures

Bone pain is the most common symptom in patients with MM, affecting nearly 70% of patients. It is usually due to collapsed vertebrae or fractured ribs but can occur almost anywhere. A fractured rib inhibits lung movement leading to pneumonia and which in turn leads to coughing and further fractured ribs. Treatment consists of adequate analgesia, local radiotherapy and systemic chemotherapy, the latter two of which can take 3-6 weeks to be effective. Opiates remain the analgesic of choice because NSAIDs can be associated with renal failure.

Localised bone lesions may present as palpable painful plasmacytomas without associated fractures especially on the skull, clavicles, and sternum, and ribs. Local radiotherapy is particularly effective in these instances.

When pathological fractures occur they are usually in the long bones like humeri or femora and may require prophylactic stabilisation, internally or externally and radiotherapy. It is an indication to start systemic chemotherapy sooner (during post-operative period) rather than later. With the spine, decompression may be needed and new techniques such as vertebroplasty or kyphoplasty are increasingly being used early. This is so important for patients to be able to maintain quality of life by not losing height and the also helps pain control by preventing mechanical compression of the nerve roots.

Hypercalcemia

Standard routine hydration with forced diuresis and steroids are required with accurate assessment of whether the patient has already developed oliguric renal failure and / or has severe sepsis. Patients should be treated with a bisphosphonate like Pamidronate or Zoledronic acid. Patients with renal impairment may need ibandronic acid. Some patients with resistant hypercalcemia may need salmon calcitonin to bring the calcium levels down.

Management of Multiple Myeloma

Initial / induction chemotherapy for new patients

Oral melphalan was first used for treating myeloma nearly half a century ago and in combination with prednisolone has become standard practice for some (usually elderly) patients ever since, with a response rate of 40-60% and median survival of about 24-30 months. This has now been combined with thalidomide and the regimen (MPT: melphalan, prednisolone and thalidomide) is the standard regimen in various European centres for elderly patients.

A radical breakthrough in MM treatment occurred when it was apparent that drugs like vincristine and adriamycin when infused over a 4 day period may be much more effective in controlling these slowly dividing malignant cells. For example, the regimens of continuous infusions over 4 days of vincristine, and adriamycin with methylprednisolone / dexamethasone (VAMP/VAD) with or without cyclophosphamide (C-VAMP/C-VAD) has frequently demonstrated a response rate of 60-80%. The development of indwelling central venous catheters and ambulatory small infusional pumps, almost all patients require virtually no admission to hospital throughout the entire induction chemotherapy period. Side effects are minimal with good quality of life, most patients working if they wish although hair loss is inevitable. However, if patients become infected, neutropenic etc, they are admitted to hospital and will in general continue to receive their chemotherapy on schedule except for cyclophosphamide. Another benefit of giving the infusional chemotherapy as intensively as possible is that like acute leukaemia, rapid early response is associated with a good long-term outcome.

Other programs of induction therapy being tested include the use of oral dexamethasone with cyclophosphamide and thalidomide (CTD), thalidomide-dexamethasone, liposomal doxorubicin in various combinations. The MRC Myeloma IX trial from the UK Medical Research Council (MRC) is currently randomising patients to CTD versus C-VAMP for initial therapy in the intensive treatment arm. However, many clinicians in a non-trial setting are using thalidomide-dexamethasone as initial therapy now.

High-dose chemotherapy / consolidation therapy

Once patients have attained maximum response to initial chemotherapy, a different strategy of treatment is required to obtain further disease control because at this point, only about a quarter of the patients are in CR and even these would be expected to relapse sooner rather than later if left without further treatment.

The standard type of treatment now given to MM patients under the age of 70 years is initial induction chemotherapy (in the form of oral drugs like CTD or infusional chemotherapy like C-VAMP) followed by high-dose melphalan 200mg/m² using peripheral blood stem cell support as rescue. Usually, the patient will then be kept in hospital for a 3-4 week period because of neutropenia following high-dose therapy. They will almost certainly require intravenous antibiotics and other haemopoietic support but increasingly much or all of this treatment may be done in day-case units. The mortality of such a procedure is less than 1% and is now being extended to patients older than 70 years and those in renal failure.

The randomised trial published by the French group (Attal et al, NEJM 1996) IFM 90 randomised patients younger than 65 years to high-dose chemotherapy with autologous bone marrow support after 4-6 cycles of induction chemotherapy versus chemotherapy alone (for total of 12 months). High-dose-therapy significantly improved the response rate (38% versus 14%; $P < 0.001$). The 7-year EFS and OS were 8% and 25% respectively in the conventional chemotherapy arm compared to 16% and 43% in the high-dose arm. Late follow-ups have indicated that high-dose therapy significantly improved both for EFS ($P = 0.01$) and OS ($P = 0.03$).

The MRC Myeloma VII Trial also randomly assigned 407 patients with previously untreated MM younger than 65 years of age to receive either standard-dose chemotherapy or high-dose therapy and autologous stem-cell transplant. The results showed the rates of CR were higher in the high-dose therapy group (44% vs. 8%, $P < 0.001$), and the intention-to-treat analysis showed a higher rate of overall survival ($P = 0.04$) and progression-free survival ($P < 0.001$) in the high-dose therapy arm. As compared with standard chemotherapy, high-dose therapy increased median survival by almost 1 year (54.1 months (95%CI, 44.9-65.2) vs. 42.3 months (95%CI 33.1 to 51.6)).

Whether this high-dose therapy should be done immediately after induction or at relapse was also evaluated by the French Myeloma Autogreffe group (MAG) and they showed that patients who were autografted early had a significantly superior EFS, longer symptom-free period or time without treatment, and a better quality of life.

It seems at first sight obvious that if one transplant is good, two (tandem) transplants must be better, but factored into this is the possibility of benefit offset by increasing potentially fatal toxicity. Thus, should a second be done at all and if so, done in tandem or delayed until relapse. The randomised study by the French group for patients under the age of 60 years whereby the patients were randomised to receive a single autotransplant with melphalan 140mg/m² and TBI (total body irradiation) 8Gy or a double autologous transplant, the first prepared with melphalan 140mg/m² and the second with melphalan-TBI. All patients were initially treated with three cycles of VAD. The results showed that 81% of patients received the first transplant and 75% in the tandem transplant arm received the second transplant. There was a significant survival benefit with tandem transplants, though this became clear after a longer follow-up suggesting that tandem transplants are possibly better for better risk patients.

The question still remains open that the tandem transplants are superior to a single transplant followed by a second autograft being undertaken at a later date. The reason this is important is that we know a proportion of patients who receive a single autograft become very long term survivors and these patients will be spared a second transplant. To determine if optimum selection of who receives a second transplant at a later date is a strategy worth pursuing. Allogeneic transplants (full conditioning or reduced intensity conditioning) are considered in a selected group of patients.

Maintenance therapy

Interferon

Interferons in patients with MM have been used as maintenance treatment post high-dose therapy to prolong the remission duration and thus overall survival. A meta-analysis of up to 24 randomised trials in MM patients by two independent groups showed a weak but definite benefit. Prolongation of survival was at best 7 months but this is important because it is the first convincing demonstration of a truly biological agent working. It seems likely that it would be most effective at time of minimal disease and in the case of MM this would correspond to post-high-dose therapy. Pegylated interferon is now available and has better patient compliance and better tolerability than interferon may lead to larger gains in terms of survival.

Thalidomide

Thalidomide is currently being trialed for use as maintenance strategy for patients with MM. This is also being used for initial therapy in combination with various alkylating agents and steroids.

Response assessment post-treatment for MM patients

Modern treatments for patients with MM are aimed at obtaining CR. This is important because it is a surrogate marker of quality of life, an independent prognostic factor for survival and is a platform for potentially curative treatments. The definition of CR has been refined since its first description 20 years ago and at present consists of absence of monoclonal paraprotein in serum and urine by immunofixation maintained for a minimum of 6 weeks, less than 5% plasma cells in bone marrow aspirate and trephine biopsy, no increase in number or size of lytic bone lesions and disappearance of soft tissue plasmacytomas. Immunofixation rather than immunoelectrophoreses is a central pre-requisite because of its reproducibility, sensitivity and prognostic significance. A new and important development has been the measurement of serum free light chain using sensitive automated immunoassays and may replace paraprotein immunofixation to follow patient's progress when in CR. Most centres currently follow the European Bone Marrow Transplant (EBMT), International Bone Marrow Transplant Registry (IBMTR) and Autologous Blood and Marrow Transplant Registry (ABMTR) criteria for response assessment (Blade et al, 1998). The International Myeloma Working Group (IMWG) has recently developed response criteria as well but these have not been validated.

Activity 2 (allow 30 + minutes)

Task 1: A 79 year old fit patient has presented with multiple myeloma. Consider how you would manage this patient.

Allow 30 minutes

- Perform a PubMed search on induction therapy and multiple myeloma
- Read a review article on the management of multiple myeloma.

Task 2: Review national and international guidelines on multiple myeloma.

Allow 30 minutes

Thinking Point:

- Would you consider the patient for treatment?
- Which chemotherapy would you consider treating the patient with?
- Would you consider maintenance therapy and if so which one?

Resources required to complete this activity

Useful websites

Pubmed

www.pubmedcentral.nih.gov

NICE National Institute for Clinical Excellence

<http://www.nice.org.uk/guidance/index.jsp?action=byTopic&o=7171>

The National Comprehensive Cancer Network (NCCN)

www.nccn.org

The British Committee for Standards in Haematology (BCSH)

www.bcsghguidelines.com

Activity 3 (allow 30 + minutes)

Task 1: You have been asked to consider a 60-year old fit patient with multiple myeloma for high-dose chemotherapy with autologous stem cell transplant. The patient is in complete remission after initial therapy.

Allow 30 minutes

- Perform a PubMed search on the management of multiple myeloma with high-dose chemotherapy with autologous stem cell transplant

Thinking Point:

- Would you consider the patient for a transplant?
- Would you consider for one or two autologous stem cell transplants?
- Would you consider maintenance therapy and if so which one?
- Which treatment would you consider at relapse?

Resources required to complete this activity

Background reading

Response criteria

Blade J, Samson D, Reece D et al. (1998) Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. British Journal of Haematology. 102: 1115-1123.

Durie BG, Harousseau JL, Miguel JS et al. (2006) International uniform response criteria for multiple myeloma. Leukemia. 20(9): 1467-73.

Induction and overall management of multiple myeloma

Sirohi B and Powles R. (2001) International Myeloma Grand Round. Lancet Oncology. 2:571-579.

Sirohi B, Powes R. (2004) Multiple Myeloma. Lancet. 363: 875-887.

[Singhal S, Mehta J, Desikan R et al. \(1999\) Antitumor activity of thalidomide in refractory multiple myeloma. New England Journal of Medicine. 341: 1565-1571.](#)

[Attal M, Harousseau JL, Leyvraz S et al \(2006\) Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. Blood 108\(10\): 3289-3294.](#)

Palumbo A, Bringhen S, Caravita T, et al. (2006) Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. Lancet. 367(9513): 825-831.

Rajkumar SV, Blood E, Vesole D, Fonseca R, Greipp PR; Eastern Cooperative Oncology Group. (2006) Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. Journal of Clinical Oncology.24(3): 431-436.

High-dose chemotherapy

[Barlogie B, Jagannath S, Desikan KR et al. \(1999\) Total therapy with tandem transplants for newly diagnosed multiple myeloma. Blood. 93: 55–65.](#)

[Attal M, Harousseau JL, Stoppa AM et al. \(1996\) Prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. New England Journal of Medicine. 355: 91–97.](#)

[Attal M, Harousseau JL, Facon T, et al. \(2003\) Single versus double autologous stem-cell transplantation for multiple myeloma. New England Journal of Medicine. 349\(26\): 2495-2502.](#)

Koreth J, Cutler CS, Djulbegovic B et al. (2007) High-dose therapy with single autologous transplantation versus chemotherapy for newly diagnosed multiple myeloma: A systematic review and meta-analysis of randomized controlled trials. Biology of Blood and Marrow Transplantation 13(2): 183-196.

Interferons

The Myeloma Trialists' Collaborative Group (MTCG). (2001) Interferon as therapy for multiple myeloma: an individual patient data overview of 24 randomised trials with over 4012 patients. *British Journal of Haematology*. 113: 1020-1034.

Sirohi B, Powles R, Lawrence D et al. (2007) An open, randomized, controlled, phase II, single centre, two-period cross-over study to compare the quality of life and toxicity experienced on PEG interferon with interferon- α 2b in patients with multiple myeloma maintained on a steady dose of interferon- α 2b. *Annals of Oncology*. 18(8): 1388-1394.

Novel drugs

Various new classes of drugs currently in clinical trials include immunomodulatory drugs, proteasome inhibitors, arsenic trioxide, interleukin-1 receptor antagonists, cyclic depsipeptides, farnesyltransferase inhibitors, p38 mitogen activated protein kinase (MAPK) inhibitor, modifiers of histone acetylation, heat shock protein inhibitors including KOS-953, direct AKT-targeting agents and monoclonal antibodies as well as passive and active immuno-therapeutics (either given alone or in combination with established therapies).

In the UK, The National Institute of Clinical Excellence (NICE) recently recommended the use of Bortezomib in patients with relapsed MM. It has recommended that all suitable MM patients should be offered treatment with Bortezomib and patients showing a full or partial response to the drug should be kept on it and funded by the National Health Service. Patients showing a minimal or no response should be taken off the drug, and the drug costs refunded by the drug's manufacturer. Hence, patients with stable disease will stop the drug. The draft recommendations followed an evaluation of a refund scheme put forward by the drug's manufacturer. The final decision on whether to put the refund scheme into practice rests with the manufacturer and the Department of Health.

Background reading

Novel drugs

[Richardson PG, Sonneveld P, Schuster MW, et al \(2005\) Bortezomib or high dose dexamethasone for relapsed multiple myeloma. *New England Journal of Medicine*. 352\(24\): 2487 -2498.](#)

Dimopoulos M, Spencer A, Attal M, et al. (2007) Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *New England Journal of Medicine*. 357(21):2123-2132.

Mitsiades CS, Hayden PJ, Anderson KC, Richardson PG. (2007) From the bench to the bedside: emerging new treatments in multiple myeloma. *Best Practice & Research: Clinical Haematology*. 20(4): 797-816.

Supportive therapy in Multiple Myeloma

Bisphosphonates

Bone destruction at any site is the cause of significant morbidity in patients with myeloma. Patients in remission have bone healing but when they relapse, a significant proportion have progressive bone disease as a terminal problem, therefore symptom control of bone disease is central to the management of all stages of MM.

Biophosphonates like Pamidronate (i/v), Zoledronate (i/v) and Ibandronate (i/v and oral) have become part of routine practice since they significantly improve QoL from preventing skeletal events. Most patients while undergoing treatment remain on bisphosphonates, the exact duration of continuation of these remains under debate. Most centres would continue for at least two years if patients remain in remission. For patients with accompanying loss of bone density, these continue for longer periods.

Osteonecrosis of Jaw (ONJ) has emerged as an adverse effect of long-term bisphosphonate therapy. Physicians need to be aware of this potentially serious complication and should practice vigilant monitoring of MM patients who are currently receiving any form of bisphosphonate therapy

Repeated infections

I/v immunoglobulin therapy must be considered for patients with repeated life-threatening infections. Consider Pneumovax and influenza vaccine. If the patient is on high-dose steroid therapy, consider either Pentamidine/Septin prophylaxis for pneumocystis carinii, antifungal and herpes prophylaxis. Consider herpes zoster prophylaxis for patients treated with single agent bortezomib.

Prophylactic anticoagulation

Prophylactic anticoagulation is recommended for patients receiving thalidomide-based or lenalidomide with dexamethasone therapy.

Support groups

Increasingly patients are being encouraged to be involved not only in their treatment decisions but also in the shape of service and research delivery. To this end, the Multiple Myeloma Research Foundation (<http://www.multiplemyeloma.org>) organises a variety of patient-family seminars and support sessions worldwide and has an international think-tank directing research strategies. The UK Myeloma forum does the same (<http://www.ukmf.org.uk>).

Activity 4 (continuous involvement over several weeks)

Discussion Board

The discussion board is a forum in which you can exchange ideas with other participants. This activity relates to the work you will have completed in earlier tasks and provides an opportunity for you to explore the difference in perspectives between the participants.

Discussion Board

When will it take place

For a 3 month period from date of publication of this article.

Which discussion thread

Management of Multiple Myeloma

What is expected of you as a participant

This module has provided an overview of the management of multiple myeloma and presenting complaints. In particular, consider the following questions:

- How would you manage the specific complications related to myeloma?
- How do you manage patients with Stage I multiple myeloma?

- What supportive care can you provide patients with multiple myeloma with crumbling bone disease?

Summary of this module

For patients with MM, it is important that treatment decision form part of a multidisciplinary team comprising a haemato-oncologist, clinical oncologist (radiotherapy), interventional radiologist (for consideration of early vertebroplasty if required), radiologist, histopathologist, renal physician and bone marrow transplant director. Entry to national clinical trials must be encouraged. There is a group of MM patients who remain in long-lasting CR for more than 10 years (post high-dose therapy), lead a normal quality life and are free from symptoms relating to MM and they are in a plateau of survival. Treatment strategies today aim to attain this. Data on the newer biological agents looks promising but long-term follow-up data with these is still awaited.

There have been developments and delivery of service and drug development recently that would have been undreamt of 10 years ago but we do realise that the biggest challenge for the next decade will be coordinating the availability of these new drugs into a background of increasingly severe financial restraints.

Key thinking points

1. Patients should be considered for entry into a clinical trial if eligible.
2. For patients with asymptomatic stage I myeloma or smouldering myeloma with no end-organ damage, a watch and wait strategy must be adopted.
3. If a patient is considered eligible for an high-dose therapy and autologous stem cell transplant, then stem cell sparing agents are to be used for induction therapy (avoid melphalan and high-doses of cyclophosphamide)
4. For induction therapy prior to high-dose therapy and an autologous stem cell transplant, it is not possible to recommend any of the regimens but infusional chemotherapy may be favoured for rapidly progressing aggressive MM to attain a quick response. Use of cyclophosphamide-thalidomide –dexamethasone vs CVAMP is currently being assessed in the MRC Myeloma IX trial. Lenalidomide with dexamethasone may be considered within a trial setting.
5. For patients ineligible for high-dose therapy and an autologous stem cell transplant, melphalan-prednisolone with thalidomide (MPT) should be considered for 12 cycles.
6. Early high-dose therapy and an autologous stem cell transplant is recommended for fit young patients
7. A recent meta-analysis has postulated that it is not unreasonable to consider other treatment options in patients fit for high-dose therapy and an autologous stem cell transplant but this included published data not individual patient data. Also, currently there is no long term data available on the use of novel agents in new patients with MM, hence it is not possible to deviate from the time tested strategy of attaining at least some long-term survival (30%).
8. Tandem or double high-dose therapy and an autologous stem cell transplant may be considered in some high-risk patients though with the availability of novel drugs this may be reserved more for patients who have relapsed when other options for treatment have

been used up. A second transplant may be considered for those patients who do not attain CR with the first transplant to maximise the chances of “operational cure”.

9. Use of interferon maintenance has been given up in most centres but with the availability of pegylated interferon which is better tolerable with better compliance and less toxicity, this may possibly be revisited.
10. No long term data is currently available for maintenance therapy with novel drugs. There are randomised trials comparing thalidomide versus placebo but the long term results are awaited.

On completion of this module you will have had the opportunity to:

By completing this module you should have a broad overview of multiple myeloma and understand how decisions are made in the management.

You will have had the opportunity:

- To understand the diagnosis of multiple myeloma and the concept of staging
- To be able to manage the disease-related complications which need urgent referral and treatment
- To gain an awareness of the different treatment modalities for multiple myeloma
- To explore the different treatment decisions that a patient can make.

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Table 1: Diagnosis of Multiple Myeloma – Investigations

Site	Test	Look for
Blood	Serum IE and IF	Paraprotein or 'M' component – 53% IgG, 20% IgA, 20% light-chain
	Immunoglobulin profile β_2 M	Immuneparesis High > 2.5 mg/L
	Serum free light chain assay	Altered kappa/lambda ratio
	Biochemistry	Haematology Low platelets and haemoglobin, high ESR, plasma cells in peripheral blood. Serum viscosity High creatinine, urea, uric acid, LDH, CRP, calcium, Albumin <40mmol/L
Urine	IE and IF	Bence-Jones, 24 hour proteinuria
Bone Marrow	Aspirate	Plasma cells- morphology, cytogenetics, FISH
	Trephine	Cellularity, amyloid , MVD (angiogenesis)
Bones	Skeletal Survey	Osteolytic lesions
	DEXA scan	Osteoporosis, bone healing
	CT/MRI	If needed for plasmacytomas
Whole body	Serum amyloid Protein (SAP)	Amyloid load
	Scan	

IE: Immunoelectrophoreses; IF: Immunofixation; β_2 M :beta-2-microglobulin; DEXA: Dual energy X-ray absorptiometry; MVD- Microvascular density;LDH: Lactate dehydrogenase; CRP-C-reactive protein; FISH: fluorescence in situ hybridisation; MRI: Magnetic resonance imaging; CT: computerised tomography

Table 2: Differentiating features between MGUS, solitary plasmacytoma, smouldering myeloma, myeloma and plasma cell leukaemia

Characteristic	MGUS	Solitary plasmacytoma	Smouldering (pre-treatment)	Multiple Myeloma	Plasma cell Leukaemia
Serum Paraprotein	IgG <35g/L IgA < 20g/L Bence-Jones protein ≤ 1 g/day	present in 50% cases	>30g/L	Variable concentration	Variable concentration
Marrow plasma cells	<10%	<5%	≥10%	≥10%	40-95%
BJP	Rare	May be present	May be	50% cases	75-90%
Immunoparesis	Rare	Rare	May be	>95% cases	Majority
Lytic bone lesions	Absent	Present (Solitary)	Absent	Present	Present
Anaemia	Absent	Absent	Absent	80%	80%
Renal dysfunction	Absent	Absent	Absent	25% cases	75%
Hypercalcemia	Absent	Absent	Absent	20%	40%
Symptoms	Absent	Local bone pain	Absent	Frequent	Frequent
PCLI	<0.5%	<1%	<1%	>1%	>1%
Treatment	None, observe 4-6 monthly	Radiotherapy with regular follow-up	None, observe closely monthly	Aggressive therapy	Aggressive therapy

PCLI: Plasma cell labelling index; BJP: Bence-Jones Proteinuria;

Table 3: Protein chemistry

β2-Microglobulin (β2M)	β2M is a protein that has recently been used as the corner-stone for predicting outcome for MM, it is a parameter included in most publications and yet paradoxically it doesn't appear in any formal generally accepted staging system (Durie-Salmon). It has a low molecular weight (MW 11,000) and is found on surface of all nucleated cells, representing the light chain of the HLA class I histocompatibility antigen complex and is excreted in the urine. In MM patients, β2-M serum levels correlate with disease activity and is an essential component (ISS) in current staging (Table 3). It also increases in renal failure, itself a poor prognostic criteria in MM patients. In most reported studies. β2-M above 5 mg/L, identifies a subgroup of patients with a median survival of only 2 years. β2-M is helpful in monitoring the course of disease unless the patients are on maintenance interferon as β2-M levels are elevated in patients on interferon even if the patients are in CR.
C-reactive protein (CRP)	CRP is an acute phase reactant whose synthesis by human hepatocytes is induced by IL-6 which is an important cytokine in myeloma cell growth. Serum CRP levels reflect IL-6 activity as infusion of anti-IL 6 monoclonal antibodies in myeloma decreases CRP levels. It is a disappointment that there have been no major publication relating to CRP as part of recent staging system but re-evaluation of CRP in patients with myeloma at diagnosis who receive modern treatment may turn out to be an important independent prognostic factor that can be linked to serum IL-6 levels.
Lactate dehydrogenase (LDH)	LDH activity is central to lymphoma practice but has not found a place in the routine management of MM because it only reflects aggressive disease which is obvious clinically. However, reassessment as an independent marker of prognosis at diagnosis warrants further assessment.