Myeloma in adults: diagnosis and management

NICE guideline: short version

Draft for consultation, August 2015

This guideline covers the diagnosis and management of myeloma in people aged over 16. The guideline also makes recommendations on diagnosis and follow-up for people with smouldering myeloma. As myeloma and myeloma treatment can cause a wide range of complications, the guideline covers many aspects of supportive care, including preventing and managing bone disease, managing neuropathy and preventing thrombosis and infection. The services that hospitals that treat myeloma should provide for adults aged over 18 are also covered.

Who is it for?

- People with myeloma, their families and carers.
- Commissioners of specialised services.
- Hospitals that provide myeloma management.
- Healthcare professionals responsible for diagnosing and managing myeloma.

This version of the guideline contains the recommendations, context and recommendations for research. The Guideline Committee's discussion and the evidence reviews are in the full guideline.

Other information about how the guideline was developed is on the project page. This includes the scope, and details of the Committee and any declarations of interest.

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Recommendations

People have the right to be involved in discussions and make informed decisions about their care, as described in Your care.

Making decisions using NICE guidelines explains how we use words to show the strength of our recommendations, and has information about safeguarding, consent and prescribing medicines (including 'off-label' use).

1.1 Communication and support

1.1.1 Provide information and support to people with myeloma or primary plasma cell leukaemia and their family members or carers (as appropriate) at diagnosis, at the beginning and end of each treatment, at disease progression and at transition to end of life care.

1.1.2 Consider providing the following information in an individualised manner to people with myeloma and their family members or carers (as appropriate):

- the disease process, relapse and remission cycle, and the person's overall prognosis
- the treatment plan, including (if appropriate) the process and the potential benefits, risks and complications of stem cell transplantation
- symptoms of myeloma and treatment-related side effects (including steroid-related side effects, infection and neuropathy)
- lifestyle measures to optimise bone health and renal function
- how to identify and report new symptoms (especially pain and spinal cord compression)
- the role of supportive and palliative care
- how to access peer support and patient support groups.

1.1.3 Offer prompt psychological assessment and support to people with myeloma at diagnosis and (as appropriate) at the beginning and

end of each treatment, at disease progression and at transition to end of life care.

1.1.4 Refer people who are assessed as needing further psychological support (see recommendation 1.1.3) to psychological services.

1.1.5 Advise family members or carers (as appropriate) about available support services at diagnosis, at the beginning and end of each treatment, at disease progression and at transition to end of life care.

1.1.6 For guidance on communication and patient-centred care see the NICE guideline on patient experience in adult NHS services.

1.2 Laboratory investigations

Laboratory investigations for people with suspected myeloma

1.2.1 Use serum protein electrophoresis and serum-free light-chain assay to confirm the presence of a paraprotein indicating possible myeloma or monoclonal gammopathy of undetermined significance (MGUS).

1.2.2 Use serum immunofixation if serum protein electrophoresis is abnormal to confirm the presence of a paraprotein indicating possible myeloma or MGUS.

1.2.3 Do not use serum protein electrophoresis, serum immunofixation, serum-free light-chain assay or urine electrophoresis (urine Bence–Jones protein assessment) alone to exclude a diagnosis of myeloma.

1.2.4 When performing a bone marrow aspirate and trephine biopsy to confirm a diagnosis of myeloma, use morphology to determine plasma cell percentage and flow cytometry to determine plasma cell phenotype.

Laboratory investigations to provide prognostic information

1.2.5 Use the same sample for all diagnostic and prognostic tests on bone marrow, so people only have to have one bone marrow aspirate and trephine biopsy.

1.2.6 When performing a bone marrow aspirate and trephine biopsy to provide prognostic information:

- Perform fluorescence in-situ hybridisation (FISH) on CD138-selected bone marrow plasma cells to identify the adverse risk abnormalities t(4;14), t(14;16), 1q gain, del(1p) and del(17p)(TP53 deletion). Use these abnormalities alongside International Staging System (ISS) scores to identify people with high-risk myeloma.
- Consider performing FISH on CD138-selected bone marrow plasma cells to identify the adverse risk abnormality t(14;20), and the standard risk abnormalities t(11;14) and hyperdiploidy.
- Consider performing immunophenotyping of bone marrow to identify plasma cell phenotype, and to inform subsequent monitoring.
- Consider performing immunohistochemistry (including Ki-67 staining and p53 expression) on the trephine biopsy to identify plasma cell phenotype, cell proliferation and p53 deletion, to provide further prognostic information.

1.2.7 Perform serum-free light-chain assay and use serum-free light-chain ratio to assess prognosis.

1.3 Imaging investigations

Imaging for people with suspected myeloma

1.3.1 Offer imaging to all people with a plasma cell disorder suspected to be myeloma.

1.3.2 Consider whole-body MRI as first-line imaging.

1.3.3 Consider whole-body low-dose CT as first-line imaging if whole-body MRI is unsuitable or the person declines it.

1.3.4 Only consider skeletal survey as first-line imaging if whole-body MRI and whole-body low-dose CT are unsuitable or the person declines them.

1.3.5 Do not use isotope bone scans to identify myeloma-related bone disease in people with a plasma cell disorder suspected to be myeloma.

Imaging for people with newly diagnosed myeloma

1.3.6 For people with newly diagnosed myeloma or smouldering myeloma who have not had whole-body imaging with 1 of the following, consider whole-body imaging to assess for myeloma-related bone disease and extra-medullary plasmacytomas with one of:

- MRI
- CT
- fluorodeoxyglucose positron emission tomography CT (FDG PET-CT).

1.3.7 For guidance on imaging for people with suspected spinal cord compression, see the NICE guideline on metastatic spinal cord compression.

1.3.8 Consider baseline whole-body imaging with MRI or FDG PET-CT for people who have non-secretory myeloma or suspected or confirmed soft tissue plasmacytomas and have not already had 1 of these tests.

1.4 Service organisation

1.4.1 For guidance on the facilities needed to provide intensive inpatient chemotherapy and transplants for adults aged 18 and over with myeloma, and the structure and function of multidisciplinary teams

(MDTs), see the NICE cancer service guidance on improving outcomes in haematological cancers.

1.4.2 For guidance on service organisation for people younger than 18, see the NICE cancer service guidance on improving outcomes in children and young people with cancer.

1.4.3 Each hospital treating myeloma in people aged 18 and over who are not receiving intensive inpatient chemotherapy or a transplant should provide local access to:

- an MDT specialising in myeloma
- supportive and palliative care, including:
  - psychological support services
  - a 24-hour acute oncology and/or haematology helpline
  - physiotherapy
  - occupational therapy
  - dietetics
  - medical social services
  - critical care
- clinical trials via the myeloma MDT
- dental services.

1.4.4 Each hospital treating myeloma in people aged 18 and over should provide regional access through its network to:

- facilities for intensive inpatient chemotherapy or transplantation
- renal support
- spinal disease management
- specialised pain management
- therapeutic apheresis
- radiotherapy
- restorative dentistry and oral surgery
- clinical trials, in particular early phase trials.

1.5 Managing newly diagnosed myeloma

First-line treatment

NICE has developed a suite of technology appraisal guidance on myeloma. It has not been possible to develop recommendations on primary disease treatment, salvage therapy for relapsed myeloma and consolidation/maintenance therapy after primary management in this guideline due to published technology appraisals or those in development.

There is no significant new evidence that would lead to a change in the existing recommendations in the published appraisals, and following consultation with relevant stakeholders, it was decided that these appraisals should be moved to the static list, thus preserving the funding direction associated with any positive recommendations. It is therefore possible for these recommendations to be incorporated into any future clinical guideline, but they cannot be updated and replaced at this time.

Recommendations in this guideline will complement the existing technology appraisals.

For more information on the relationship between the technology appraisal and clinical guidelines programmes please see Updating technology appraisals in the context of clinical guidelines.

1.5.1 For guidance on the use of bortezomib for induction therapy, see Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation (NICE technology appraisal guidance 311).

1.5.2 Thalidomide in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma in people for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate. [This recommendation is from Bortezomib and thalidomide for the first‑line treatment of multiple myeloma (NICE technology appraisal guidance 228).]

1.5.3 Bortezomib in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma if:

- high-dose chemotherapy with stem cell transplantation is considered inappropriate and
- the person is unable to tolerate or has contraindications to thalidomide [This recommendation is from Bortezomib and thalidomide for the first‑line treatment of multiple myeloma (NICE technology appraisal guidance 228).]

First autologous stem cell transplantation

1.5.4 Consider using frailty and performance status measures that include comorbidities to assess the suitability of people with myeloma for first autologous stem cell transplant.

1.5.5 Do not use age or the level of renal impairment alone to assess the suitability of people with myeloma for first autologous stem cell transplant.

Allogeneic stem cell transplantation

1.5.6 When assessing whether people with myeloma are suitable for an allogeneic stem cell transplant, take into account:

- whether the person has chemosensitive disease
- how many previous lines of treatment they have had
- whether a fully human leukocyte antigen (HLA) matched donor is available
- how graft-versus-host disease (GvHD) and other complications will get worse with age
- the risk of higher transplant-related mortality and morbidity, versus the potential for long-term disease-free survival
- improving outcomes with other newer treatments
- the person's understanding of the risks and benefits.

Primary plasma cell leukaemia

1.5.7 Consider bortezomib-based and/or lenalidomide-based combination induction chemotherapy for people with primary plasma cell leukaemia.

1.5.8 Consider high-dose melphalan-based autologous stem cell transplantation for people with primary plasma cell leukaemia if they are suitable.

1.6 Managing acute renal disease caused by myeloma

1.6.1 Consider immediately starting a bortezomib- and dexamethasone-based combination regimen for people with untreated, newly diagnosed, myeloma-induced acute renal disease.

1.6.2 If a bortezomib-based combination regimen is unsuitable for people with untreated, newly diagnosed, myeloma-induced acute renal disease, consider immediately starting a thalidomide- and dexamethasone-based combination regimen[1].

1.6.3 Do not perform plasma exchange for myeloma-induced acute renal disease.

1.7 Preventing and managing bone disease

Preventing bone disease

1.7.1 To prevent bone disease, offer people with myeloma:

- zoledronic acid, or
- disodium pamidronate, if zoledronic acid is contraindicated or not tolerated, or
- sodium clodronate, if zoledronic acid and disodium pamidronate are contraindicated, not tolerated or not suitable.

[1] At the time of consultation (August 2015), thalidomide in combination with dexamethasone did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

1.7.2 Consider immediately referring people with myeloma for dental assessment and treatment before starting zoledronic acid or disodium pamidronate.

1.7.3 For people who need urgent myeloma treatment, consider referring for dental assessment and treatment as soon as possible after they start treatment.

Managing non-spinal bone disease

1.7.4 Offer people with myeloma and non-spinal bone disease who have not already started bisphosphonates:

- zoledronic acid, or
- disodium pamidronate, if zoledronic acid is contraindicated or not tolerated, or
- sodium clodronate, if zoledronic acid and disodium pamidronate are contraindicated, not tolerated or not suitable.

1.7.5 Assess the risk of fracture (in line with the NICE guideline on assessing the risk of fragility fractures in osteoporosis) in people with myeloma and non-spinal bone disease.

1.7.6 Consider surgical stabilisation followed by radiotherapy for non-spinal bones that have fractured or are at high risk of fractures.

1.7.7 Consider radiotherapy for non-spinal bones that have fractured or are at high risk of fracture if surgical intervention is unsuitable or not immediately needed.

1.7.8 Consider radiotherapy for people with myeloma and non-spinal bone disease who need additional pain relief if:

- chemotherapy and initial pain management has not led to prompt improvement in pain control.
- chemotherapy is unsuitable and current pain medication is not working.

1.7.9 Consider re-treatment with radiotherapy if pain recurs or if there is regrowth of a previously treated lesion.

1.7.10 Consider seeking advice from or referral to specialists in palliative care or pain medicine for people with complex non-spinal bone disease.

Managing spinal bone disease

1.7.11 For guidance on treating metastatic spinal cord compression, see the NICE guideline on metastatic spinal cord compression.

1.7.12 Offer all people with myeloma and spinal bone disease:

- bisphosphonates as follows, if not already started:
  - zoledronic acid, or
  - disodium pamidronate, if zoledronic acid is contraindicated or not tolerated, or
  - sodium clodronate, if zoledronic acid and disodium pamidronate are contraindicated, not tolerated or unsuitable
- systemic pain control, when relevant using the NICE guidelines on neuropathic pain and opioids in palliative care.

1.7.13 Consider the following as adjuncts to other treatments for all people with myeloma and spinal bone disease:

- interventional pain management
- bracing.

1.7.14 In people with radiological evidence of myeloma-related spinal instability, consider immediate intervention with:

- spinal surgery, with or without radiotherapy
- cement augmentation, with or without radiotherapy
- radiotherapy alone, if spinal intervention is unsuitable or not currently needed.

1.7.15 In people with radiological evidence of myeloma-related spinal bone disease without instability, consider:

- cement augmentation, with or without radiotherapy
- radiotherapy alone.

1.8 Preventing and managing complications

Preventing infection

1.8.1 Offer people with myeloma the seasonal influenza vaccination.

1.8.2 Consider extending the pneumococcal vaccination to people with myeloma who are under 65.

1.8.3 Consider intravenous immunoglobulin replacement therapy for people who have hypogammaglobulinaemia and/or recurrent infections.

1.8.4 Consider continuing aciclovir[2] or equivalent antiviral prophylaxis after treatment with bortezomib or other proteasome inhibitors ends.

1.8.5 Consider aciclovir[3] or equivalent antiviral prophylaxis for people who are taking both immunomodulatory drugs and high-dose steroids.

1.8.6 Consider testing for hepatitis B, hepatitis C and HIV before starting myeloma treatment.

[2] At the time of consultation (August 2015), aciclovir did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[3] At the time of consultation (August 2015), aciclovir did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

Managing peripheral neuropathy

1.8.7 Explain the symptoms of neuropathy to people with myeloma, and encourage them to tell their clinical team about any new, different or worsening neuropathic symptoms immediately.

1.8.8 If people who are receiving bortezomib develop neuropathic symptoms, consider immediately:

- switching to subcutaneous injections and/or
- reducing to weekly doses and/or
- reducing the dose.

1.8.9 Consider reducing the dose if people are taking a drug other than bortezomib and develop neuropathic symptoms.

1.8.10 Temporarily stop neuropathy-inducing myeloma treatments if people develop either of the following:

- grade 2 neuropathy with pain
- grade 3 or 4 neuropathy.

Preventing thrombosis

1.8.11 For people with myeloma who are starting immunomodulatory drugs, offer thromboprophylaxis with either:

- low molecular weight heparin (LMWH) at a prophylactic dose, or
- vitamin K antagonists at a therapeutic dose, to maintain an international normalised ratio (INR) of 2–3.

1.8.12 If LMWH or vitamin K antagonists are unsuitable, consider low-dose aspirin[4].

[4] At the time of consultation (August 2015), aspirin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

1.8.13 When starting thromboprophylaxis, assess the risk factors, contraindications and practicalities of each prophylactic strategy.

1.8.14 Do not offer fixed low-dose vitamin K antagonists for thromboprophylaxis to people with myeloma who are starting immunomodulatory drugs.

1.8.15 Consider switching thromboprophylaxis to low-dose aspirin for people who:

- are taking immunomodulatory drugs and
- have achieved maximum response and
- have no high risk factors.

Managing fatigue

1.8.16 If other treatable causes of anaemia have been excluded, consider erythropoietin analogues (adjusted to maintain a steady state of haemoglobin at 110–120 g/litre) to improve fatigue in people with myeloma who have symptomatic anaemia.

1.9 Monitoring

1.9.1 Monitor people with smouldering myeloma every 3 months for the first 5 years, and then decide the frequency of further monitoring based on the long-term stability of the disease.

1.9.2 Monitor people who have completed myeloma treatment and recovered at least every 3 months. Take into account any risk factors for progression, such as:

- high-risk fluorescence in-situ hybridisation (FISH)
- impaired renal function
- disease presentation.

1.9.3 Monitoring for myeloma and smouldering myeloma should include:

- assessment of symptoms related to myeloma and myeloma treatment and

- the following laboratory tests:
  - full blood count
  - renal function
  - bone profile
  - serum immunoglobulins and serum protein electrophoresis
  - serum-free light-chain assay, if appropriate.

1.9.4 Do not offer people with myeloma or smouldering myeloma routine skeletal surveys for disease monitoring.

1.9.5 Consider symptom-directed imaging for people with myeloma or smouldering myeloma if any new bone symptoms develop.

1.9.6 Consider whole-body MRI, spinal MRI or fluorodeoxyglucose positron emission tomography CT (FDG PET-CT) for people with myeloma or smouldering myeloma if there is serological relapse or disease progression.

1.10 Managing relapsed myeloma

First relapse

NICE has developed a suite of technology appraisal guidance on myeloma. It has not been possible to develop recommendations on primary disease treatment, salvage therapy for relapsed myeloma and consolidation/maintenance therapy after primary management in this guideline due to published technology appraisals or those in development.

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Recommendations in this guideline will complement the existing technology appraisals.

For more information on the relationship between the technology appraisal and clinical guidelines programmes please see Updating technology appraisals in the context of clinical guidelines.

1.10.1 Bortezomib monotherapy is recommended as an option for the treatment of progressive multiple myeloma in people who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation, under the following circumstances:

- the response to bortezomib is measured using serum M protein after a maximum of four cycles of treatment, and treatment is continued only in people who have a complete or partial response (that is, reduction in serum M protein of 50% or more or, where serum M protein is not measurable, an appropriate alternative biochemical measure of response), and
- the manufacturer rebates the full cost of bortezomib for people who, after a maximum of four cycles of treatment, have less than a partial response (as defined above). [This recommendation is from Bortezomib monotherapy for relapsed multiple myeloma (NICE technology appraisal guidance 129).]

1.10.2 People currently receiving bortezomib monotherapy who do not meet the criteria in recommendation 1.10.1 should have the option to continue therapy until they and their clinicians consider it appropriate to stop. [This recommendation is from Bortezomib monotherapy for relapsed multiple myeloma (NICE technology appraisal guidance 129).]

Second autologous stem cell transplantation

1.10.3 Offer a second autologous stem cell transplant to people with relapsed myeloma who are suitable and who have:

- completed re-induction therapy and
- had a response duration of more than 24 months after their first autologous stem cell transplant.

1.10.4 Consider a second autologous stem cell transplant for people with relapsed myeloma who are suitable and who have:

- completed reinduction therapy and
- had a response duration of between 12 and 24 months after their first autologous stem cell transplant.

1.10.5 When assessing whether people with relapsed myeloma are suitable for a second autologous stem cell transplant, take into account:

- response to the first autologous stem cell transplant
- International Staging System (ISS) stage
- number of prior treatments
- age, frailty and comorbidities
- adverse fluorescence in-situ hybridisation (FISH) results.

Subsequent therapy

1.10.6 For guidance on the use of lenalidomide in people who have received at least 1 prior therapy, see Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy (NICE technology appraisal guidance 171).

1.10.7 For guidance on the use of pomalidomide in people who have relapsed and refractory disease, see Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib (NICE technology appraisal guidance 338).

Terms used in this guideline

Smouldering myeloma

In this guideline, only recommendations that specifically refer to smouldering myeloma apply to this condition.

To find out what NICE has said on topics related to this guideline, see our web pages on blood and bone marrow cancers, complications of cancer and embolism and thrombosis.

Implementation: getting started

This section will be completed in the final guideline using information provided by stakeholders during consultation.

To help us complete this section, please use the stakeholder comments form to give us your views on these questions:

1. Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why.

2. What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.)

Context

Myeloma is a malignancy of the plasma cells that normally produce immunoglobulin. It affects multiple organs and systems, including the bones, kidneys, blood and immune systems.

Myeloma is the seventeenth most common cancer in the UK. In 2010, 4672 people in the UK were diagnosed with myeloma. It occurs more frequently in men and in people of African-Caribbean family origin. Diagnosis is often delayed because the symptoms are not specific to myeloma, and this leads to significant early morbidity and mortality.

Myeloma management is complex and challenging. Effective treatments have been developed over the last 15 years, and although myeloma is still incurable these treatments have led to improvements in overall survival and quality of life. However, myeloma treatment increasingly involves expensive drugs and frequent hospital visits. Complications of myeloma and myeloma treatment cause an increasing long-term strain on supportive and palliative care services, and on carers.

This guideline covers areas in which there is uncertainty or variation in practice. It contains recommendations on:

- communication and support
- laboratory investigations and imaging to diagnose myeloma and determine further treatment
- managing bone disease and acute renal disease
- autologous and allogeneic stem cell transplantation
- preventing and managing myeloma- and treatment-induced complications
- monitoring for people with smouldering myeloma and myeloma.

Because of the changes to the International Myeloma Working Group definition of smouldering myeloma, it was not possible to make any recommendations for clinical practice on managing this condition. The new definition has changed how smouldering myeloma and myeloma are differentiated, and there is currently no evidence available that is using the new definitions.

This guideline covers adults (aged 16 years and over):

- who are referred to secondary care with suspected myeloma
- with newly diagnosed or relapsed myeloma (including high-risk myeloma and primary plasma cell leukaemia).

This guideline does not cover people who have:

- a solitary plasmacytoma without myeloma
- amyloid light-chain amyloidosis in the absence of myeloma

- paraproteins secondary to other conditions.

Recommendations for research

The Guideline Committee has made the following recommendations for research. The Committee's full set of research recommendations is detailed in the full guideline.

1 Diagnostic investigations to predict treatment outcomes

A prospective randomised multi-centre trial of different treatment strategies should compare the prognostic value of the Hevylite assay and ratio with other prognostic factors and tests, including the serum-free light-chain assay and fluorescence in situ hybridisation (FISH), in people with newly diagnosed myeloma who are starting treatment. Outcomes of interest are overall response, complete response, minimal residual disease, progression-free survival, overall survival and resource use.

Why this is important

Hevylite is a new assay which some studies have indicated is a useful prognostic tool. However, it is not clear how robustly it has been evaluated against other prognostic factors and tests, or whether it is an independent prognostic factor. The Hevylite assay should be evaluated in an accredited centralised laboratory independent of links with the manufacturer.

2 Imaging investigations for newly diagnosed myeloma

Observational studies should be carried out, comparing the effectiveness of whole-body MRI, fluorodeoxyglucose positron emission tomography CT (FDG PET-CT) and whole-body low-dose CT in detecting lesions that may determine the start of treatment for people with newly diagnosed myeloma. Outcomes of interest are lesion detection, sensitivity and specificity for myeloma-related bone disease, patient acceptability, incremental upstaging, radiation exposure, risk of second primary cancer, the impact of additional information on predicting progression-free survival, overall survival and skeletal-related events.

Why this is important

Newer imaging techniques are replacing skeletal surveys for assessing myeloma-related bone disease in people with newly diagnosed myeloma. However, the most effective technique is not known.

3 Management of smouldering myeloma

A randomized multi-centre prospective trial should be carried out for patients with newly diagnosed smouldering myeloma (as defined by the International Myeloma Working Group 2014 classification) to:

- identify which combinations of FISH, molecular technologies, bone marrow plasma cell percentage, whole-body imaging, immunophenotype, serum-free light-chain levels or ratio, Hevylite, paraprotein levels, immunoparesis, and International Staging System (ISS) are most effective at risk stratification for people with smouldering myeloma.
- compare fixed duration treatment (with or without bone-directed therapy), continuous treatment (with or without bone-directed therapy) and no treatment (with or without bone-directed therapy).

Outcomes of interest are time to biochemical and/or clinical progression, overall survival, adverse events, quality of life and resource use.

Why this is important

Changes to the International Myeloma Working Group definitions of smouldering myeloma and myeloma have affected the risk stratification process for smouldering myeloma. It is unclear if the previous risk stratification approach remains valid. It is also unclear if earlier treatment will be of benefit to people with smouldering myeloma. .

4 Allogeneic stem cell transplantation

Research is needed into the effectiveness of combined autologous–allogeneic stem cell transplantation compared with autologous stem cell transplantation, plus consolidation and maintenance treatment in chemosensitive patients at first response or first relapse. Outcomes of interest are progression-free

survival, overall survival, transplant-related mortality, quality of life, early and late toxicity including graft-versus-host-disease (GvHD) and resource use. This research should be included as an option in appropriate mainstream clinical trials for myeloma.

Why this is important

There are conflicting data from a small number of studies on long-term survival following auto/allo stem cell transplantation compared with autologous stem cell transplantation. These studies were performed before thalidomide, bortezomib and lenalidomide were used as myeloma treatments. These drugs produce better responses and also have the capacity to affect immunological responses after the transplant. Research is needed to see if there is a role for auto/allo stem cell transplant in the ongoing treatment of myeloma.

5 Bisphosphonates for the prevention of bone disease

A randomised controlled trial should be carried out, comparing monthly zoledronic acid indefinitely with zoledronic acid for fixed duration in patients with myeloma. Outcomes of interest are skeletal-related events, progression-free survival, overall survival, utility of bone biomarkers, incidence of osteonecrosis of the jaw, quality of life and resource use.

Why this is important

There is good-quality evidence to support the use of zoledronic acid to prevent bone disease in people with myeloma. However, the optimal frequency and duration of treatment is not clearly defined and needs further research, particularly given the quality-of-life implications for people needing regular, life-long visits to hospital.