Complete Summary

GUIDELINE TITLE

Guidelines on the diagnosis and management of multiple myeloma 2005.

BIBLIOGRAPHIC SOURCE(S)

Smith A, Wisloff F, Samson D, UK Myeloma Forum, Nordic Myeloma Study Group, British Committee for Standards in Haematology. Guidelines on the diagnosis and management of multiple myeloma 2005. Br J Haematol 2006 Feb;132(4):410-51. [292 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- July 31, 2008, Erythropoiesis Stimulating Agents (ESAs): Amgen and the U.S. Food and Drug Administration (FDA) informed healthcare professionals of modifications to certain sections of the Boxed Warnings, Indications and Usage, and Dosage and Administration sections of prescribing information for Erythropoiesis Stimulating Agents (ESAs). The changes clarify the FDA-approved conditions for use of ESAs in patients with cancer and revise directions for dosing to state the hemoglobin level at which treatment with an ESA should be initiated.
- November 8, 2007 and January 3, 2008 Update, Erythropoiesis Stimulating Agents (ESAs): The U.S. Food and Drug Administration (FDA) notified healthcare professionals of revised boxed warnings and other safety-related product labeling changes for erythropoiesis-stimulating agents (ESAs) stating serious adverse events, such as tumor growth and shortened survival in patients with advanced cancer and chronic kidney failure.

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SCOPE

DISEASE/CONDITION(S)

Multiple myeloma

GUIDELINE CATEGORY

Diagnosis
Management

CLINICAL SPECIALTY

Hematology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To revise guidelines for the diagnosis and management of myeloma published in 2001 by the Guidelines Working Group of the UK Myeloma Forum
- To revise guidelines prepared in 1995 by the Nordic Myeloma Working Group
- To prepare a common set of updated guidelines

TARGET POPULATION

Individuals with symptomatic multiple myeloma and asymptomatic multiple myeloma with myeloma-related organ damage

INTERVENTIONS AND PRACTICES CONSIDERED

1. Investigation and diagnosis
    - International Myeloma Working Group diagnostic criteria
    - Initial investigations
        - Screening tests (full blood count [FBC], erythrocyte sedimentation rate [ESR] or plasma viscosity, serum or plasma electrolytes, urea, creatinine, calcium, albumin and uric acid, electrophoresis of serum and concentrated urine quantification of non-isotypic immunoglobulins, X-ray of symptomatic areas)

        - Tests to establish diagnosis (bone marrow aspirate ± trephine biopsy, immunofixation of serum and urine, skeletal survey)
        - Tests to estimate tumour burden and prognosis (bone marrow cytogenetics or fluorescent in situ hybridisation (FISH) analysis, quantification of monoclonal protein in serum and urine, calcium, albumin, beta2-microglobulin, skeletal survey
        - Tests to assess myeloma-related organ impairment (FBC, serum or plasma urea and creatinine, creatinine clearance (measured or calculated), calcium, albumin, lactate dehydrogenase, C-reactive protein, quantification of non-isotypic immunoglobulins, skeletal survey
        - Special test indicated in some patients (bone marrow immunohistology or flow cytometry, vitamin B_{12} and folate assays, Magnetic resonance imaging (MRI), computed tomography (CT) scan
    - Cytogenetic abnormalities
    - Paraprotein (M-protein) levels

2. Monitoring and Indications for Starting Therapy
    - M-protein levels
    - Clinical features of disease progression

3. Prognostic factors and staging in symptomatic myeloma
    - International Prognostic Index

4. Imaging Techniques
    - CT
    - MRI

5. Management
    - Pain Control
        - Systemic
        - Local (local radiotherapy, vertebroplasty kyphoplasty)
    - Hypercalcemia and bone disease (rehydration, biphosphonates, furosemide)
    - Renal impairment (consultation with nephrologist, plasma exchange, dialysis)
    - Anemia (erythropoietin)
    - Infection (broad spectrum antibiotics, prophylactic trimethoprim-sulphamethoxazole, vaccination against influenza, *Streptococcus pneumonia* and *Haemophilus influenza*, prophylactic immunoglobulin administration)
    - Neurologic complications
        - Cord compression (dexamethasone, radiotherapy)
        - Peripheral neuropathy (review by neurologist, clinical monitoring)

6. Treatment
    - Initial chemotherapy prior to high-dose therapy (vincristine, doxorubicin, and dexamethasone [VAD])
    - Conventional therapy (melphalan [or cyclophosphamide] and prednisolone)

- Chemotherapy in patients with renal failure (VAD or dexamethasone)
- Autologous stem cell transplantation
- Allogeneic stem cell transplantation
- Maintenance therapies (interferon)
- Relapsed/progressive disease (thalidomide, bortezomib)
- Late-stage disease
    - Symptom relief
    - Supportive care
    - Palliative care

7. Patient information and support
    - Written information
    - Emotional and psychological support

MAJOR OUTCOMES CONSIDERED

- Response to therapy
- Pain control
- Adverse events
- Quality of life
- Survival

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

A review of key literature to 30 November 2004 was performed, including Cochrane database, Medline and Internet searches. Key references subsequent to this date were incorporated in the final drafting where relevant.

A review of major conference reports was performed.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

Ia Evidence obtained from meta-analysis of randomised controlled trials

Ib Evidence obtained from at least one randomised controlled trial

IIa Evidence obtained from at least one well-designed, non-randomised study, including phase II trials and case-control studies

IIb Evidence obtained from at least one other type of well-designed, quasi-experimental study (i.e. studies without planned intervention including observational studies)

III Evidence obtained from well-designed, non-experimental descriptive studies. Evidence obtained from meta-analysis or randomised controlled trials or phase II studies which is published only in abstract form

IV Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Recommendations based on literature review and consensus of expert opinion.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grades of Recommendations

Grade A, Evidence level Ia and Ib Recommendation based on at least one randomised controlled trial of good quality and consistency addressing specific recommendation

Grade B, Evidence levels IIa, IIb, and III Recommendation based on well-conducted studies but no randomised controlled trials on the topic of recommendation

Grade C, Evidence level IV Evidence from expert committee reports and/or clinical experiences of respected authorities

COST ANALYSIS

Health economic data on long-term bisphosphonate use are conflicting, with no increase in overall costs observed in the Finnish clodronate study but a 17% increase in overall costs in the MRC study. A systematic review of the role of bisphosphonates in malignant disease included an economic evaluation of bisphosphonates. Analysis suggested an overall cost of £1500 per skeletal-related event (SRE) prevented, based on pamidronate 90 mg i.v. monthly for up to 4 years or until death if earlier.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

- Review by UK Myeloma Foundation (UKMF) Executive, British Committee for Standards in Haematology (BCSH) Committee and regional coordinators of the Nordic Myeloma Study Group (NMSG)
- Review by a sounding board group of 100 members of the British Society for Haematology (BSH)

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Recommendation grades (**A-C**) and levels of evidence (**Ia-IV**) are defined at the end of the "Major Recommendations" field.

Diagnosis, Investigation and Indications for Treatment

Investigation and Diagnosis

Diagnostic criteria and differential diagnosis

- The diagnostic criteria agreed by the International Myeloma Working Group should be used (**grade C recommendation; level III evidence**).
- Investigation should include the tests shown in the table below titled "Initial investigations in patients with myeloma." A careful assessment for myeloma-related organ and tissue impairment should be carried out, in order to identify asymptomatic patients who require treatment (**grade C recommendation; level III evidence**).
- Cytogenetic abnormalities have prognostic significance but should primarily be analysed within the context of clinical trials designed to elucidate their importance for choice of therapy (**grade C recommendation; level III evidence**).
- The extent of diagnostic procedures in asymptomatic patients with an M-protein should take into consideration the age of the patient, the presence of other disease and levels of M-protein (**grade C recommendation; level III evidence**).

- Skeletal survey and bone marrow examination are not mandatory to make a diagnosis of monoclonal gammopathy of undetermined significance (MGUS) in the absence of relevant clinical symptoms, anaemia, hypercalcaemia or renal impairment, but are recommended in younger patients and may be considered for older patients with M-protein levels above 20 g/L (**grade C recommendation; level III evidence**).
- Clinical review and repeat measurements of paraprotein levels at 3 and 6 months are advised to establish a firm diagnosis of MGUS (**grade C recommendation; level III evidence**).

Initial Investigations in Patients with Myeloma

Screening Tests	Tests to establish diagnosis	Tests to estimate tumour burden and prognosis	Tests to assess myeloma-related organ impairment	Special tests indicated in some patients
FBC, ESR or plasma viscosity	Bone marrow aspirate ± trephine biopsy	Bone marrow cytogenetics or (FISH) analysis	FBC (anaemia)	Bone marrow immunohistology or flow cytometry Vitamin B_{12} and folate assays*
Serum or plasma electrolytes, urea, creatinine, calcium, albumin and uric acid Electrophoresis of serum and concentrated urine Quantification of non-isotypic immunoglobulins	Immunofixation of serum and urine	Quantification of monoclonal protein in serum and urine Calcium Albumin Beta2-microglobulin	Serum or plasma urea and creatinine Creatinine clearance (measured or calculated) Calcium Albumin Lactate dehydrogenase C-reactive protein Quantification of non-isotypic immunoglobulins	
X-ray of symptomatic areas	Skeletal survey**	Skeletal survey	Skeletal survey	Magnetic resonance imaging (MRI) Computed tomography scan

FBC, full blood count, ESR, erythrocyte sedimentation rate, FISH, fluorescent *in situ* hybridization

*Where there is macrocytosis (not uncommon in myeloma)

**Recommendations for skeletal survey are given below

Monitoring and indications for starting therapy

- Monitoring of patients with MGUS and asymptomatic myeloma should be indefinite; frequency may vary according to the risk of progression, MGUS with high M-protein levels and asymptomatic myeloma being associated with the highest risk (**grade B recommendation; level III evidence**).
- Monitoring of asymptomatic myeloma should include regular (usually three monthly) clinical assessment and measurement of both serum and urinary paraprotein. Repeat bone marrow examinations and skeletal X-rays will be required less often or when new symptoms or signs develop (**grade C recommendation; level IV evidence**).
- Monitoring of MGUS similarly should include regular clinical assessment and follow-up measurement of serum paraprotein; six monthly or annual will usually be sufficient in those with low risk of progression (**grade C recommendation; level IV evidence**).
- Patients and general practitioners should be provided with information on risk and clinical features of disease progression, particularly those listed in Table VI of the original guideline document (**grade C recommendation; level IV evidence**).
- Treatment should be deferred until there is evidence of disease progression or organ impairment (**grade A recommendation; level Ib evidence**).
- Patients without clinical symptoms but with radiological evidence of bone disease should commence treatment immediately (**grade B recommendation; level IIb evidence**). These patients are now grouped with symptomatic myeloma.

Prognostic Factors and Staging in Symptomatic Myeloma

- The International Prognostic Index based on serum albumin beta2-microglobulin is recommended in preference to the Durie/Salmon staging system (**grade C recommendation; level IV evidence**).
- Prognosis should be evaluated before starting treatment, requiring, as a minimum, serum levels of beta2-microglobulin and albumin. Cytogenetic and/or fluorescence in situ hybridisation analysis may be helpful if available. These, however, should be interpreted with caution in individual patients (**grade C recommendation; level IV evidence**).
- At present there is no evidence to support using prognostic factors to choose therapy in individual patients (**grade C recommendation; level IV evidence**).

The Use of Imaging Techniques in Myeloma

Diagnosis

- Skeletal survey should be part of the staging procedure of newly diagnosed myeloma patients and should include a postero-anterior (PA) view of the chest, antero-posterior (AP) and lateral views of the cervical spine (including an open-mouth view), thoracic spine, lumbar spine, humeri and femora, AP and lateral view of the skull and AP view of the pelvis. In addition, any symptomatic areas should be specifically visualised with appropriate views (**grade C recommendation; level IV evidence**).

- Computed tomography (CT) should be used to clarify the significance of ambiguous plain radiographic findings, such as equivocal lytic lesions, especially in parts of the skeleton that are difficult to visualize on plain radiographs, such as ribs, sternum and scapulae (**grade B recommendation; level III evidence**).
- CT should also be used to examine symptomatic areas of the skeleton where no pathological lesion is found on the skeletal survey (**grade B recommendation; level III**).
- CT or magnetic resonance imaging (MRI) is indicated to delineate the nature and extent of soft tissue disease and these two imaging techniques can give complementary information (**grade B recommendation; level III evidence**).
- Tissue biopsy may be guided where appropriate by CT scanning (**grade B recommendation; level III evidence**).
- MRI is the technique of choice for investigation of patients with a neurological presentation suggestive of cord compression (**grade B recommendation; level IIB evidence**).
- MRI of the whole spine should be performed in patients with an apparently solitary plasmacytoma of bone irrespective of site of the index lesion (**grade C recommendation; level IV evidence**).
- Bone scintigraphy has no place in the routine investigation of myeloma (**grade C recommendation; level IV evidence**).
- Dual energy X-ray absorptiometry (DEXA) scanning has no role in the routine management of myeloma (**grade C recommendation; level IV evidence**).

Imaging in the Monitoring of Disease

- Any newly symptomatic areas of the skeleton should be specifically targeted for repeat/follow-up imaging (**grade C recommendation; level III evidence**).
- CT or MRI should be employed for evaluation of symptomatic areas where plain radiographs are negative (**grade B recommendation; level III evidence**).
- MR and positron emission tomography (PET) scanning may aid disease evaluation in individual patients (**grade C recommendation; level III evidence**).

Pain Control

Systemic Analgesia

- An analgesic appropriate to the severity of the pain should be used (**grade C recommendation; level III evidence**).
- Non-steroidal anti-inflammatory drugs should be avoided (**grade C recommendation; level III evidence**).
- Analgesics should be given regularly (**grade C recommendation; level III evidence**).
- Oral analgesia is preferable where possible (**grade C recommendation; level III evidence**).
- Side effects should be actively managed (**grade C recommendation; level III evidence**).

- Analgesic requirements should be regularly recorded (**grade C recommendation; level III evidence**).
- Additional non-analgesic drugs should be considered in individual circumstances (**grade C recommendation; level III evidence**).
- Other methods of pain control must be considered in all patients (**grade C recommendation; level III evidence**).

Local Analgesic Approaches

- Local radiotherapy is helpful for pain control; a dose of 8 Gy single fraction is recommended (**grade C recommendation; level III evidence**).
- Long bone fractures require stabilisation and subsequent radiotherapy; a dose of 8 Gy single fraction is recommended (**grade C recommendation; level III evidence**).
- The use of vertebroplasty or kyphoplasty may be considered in patients with persistent pain (**grade C recommendation; level III evidence**).
- The use of kyphoplasty should follow the National Institute for Health and Clinical Excellence (NICE) recommendations summarised (section 4.2.5 of the original guideline document) (**grade C recommendation; level III evidence**).

Hypercalcaemia and Bone Disease

Hypercalcaemia

- In mild hypercalcaemia (corrected calcium 2.6–2.9 mmol/L) rehydrate with oral fluids (**grade C recommendation; level III evidence**).
- In moderate-severe hypercalcaemia (corrected calcium $\geq$-2.9 mmol/L) rehydrate with intravenous fluids and give furosemide if required (**grade C recommendation; level III evidence**).
- If not already on a bisphosphonate, start bisphosphonate immediately (**grade C recommendation; level III evidence**).
- If already on a bisphosphonate, consider changing to a more potent bisphosphonate or increasing the dose (**grade C recommendation; level III evidence**).
- Additional therapy may be required in refractory patients (**grade C recommendation; level III evidence**).

The Role of Bisphosphonates

- Bisphosphonate therapy is recommended for all patients with myeloma requiring chemotherapy, whether or not bone lesions are evident (**grade A recommendation; level Ib evidence**).
- Treatment should be continued for at least 2 years (**grade A recommendation; level Ib evidence**); it is current practice to continue treatment indefinitely although there are a few reported data on longer-term use.
- Oral clodronate (1600 mg/day or equivalent dosage according to formulation), intravenous pamidronate, and intravenous (i.v.) zoledronic acid (**grade A recommendation; level Ib evidence**) may be used. Monthly i.v. pamidronate 90 mg and zoledronic acid 4 mg are equivalent in efficacy

(**grade A recommendation; level Ib evidence**). The choice of therapy will depend on patient and physician preference.
- Doses, infusion times and frequencies should be as recommended by the manufacturer, and renal function should be monitored. Creatinine should be checked before each zoledronic acid infusion.
- Special caution is required with all bisphosphonates in patients with moderate to severe renal failure; zoledronic acid should not be used if creatinine is >265 micromol/L.
- There are insufficient data to make a recommendation for the use of bisphosphonates in patients with asymptomatic myeloma.

Renal Impairment

Early Management of Renal Failure

Initial management of renal failure should include vigorous rehydration and treatment of infection.

- Patients with hypercalcaemia not responding to rehydration alone should be treated with an intravenous bisphosphonate.
- Seek the advice of a nephrologist if renal failure does not improve within 48 hours.
- Consider plasma exchange, where possible within the context of a clinical trial.
- Dialysis should be offered to patients, where appropriate for the management of the renal failure.

Management of Anemia

- In newly diagnosed patients, erythropoietin (EPO) should usually not be considered before response to chemotherapy has been assessed (**grade C recommendation; level IV evidence**).
- A therapeutic trial of EPO may be considered in patients with symptomatic anaemia receiving chemotherapy (**grade A recommendation; level Ib evidence**). As part of the basis for this consideration, serum EPO concentration should be measured. A serum EPO >200 International Units (IU)/ml, a high transfusion requirement and a low-platelet count are negative prognostic factors for a response to EPO.
- The dose should be doubled if there is no sign of effect after 4–6 weeks (**grade B recommendation; level IIa evidence**).
- The probability of effect is low if hemoglobin (Hb) has not risen by 1–2 g/dL after 6–8 weeks and EPO should then be stopped (**grade B recommendation; level IIb evidence**).
- EPO should be stopped or the dose reduced when Hb rises above 12 g/dL (**grade C recommendation; level IV evidence**).
- EPO may also be considered in patients not receiving chemotherapy who have symptomatic anaemia (**grade B recommendation; level IIa evidence**).
- Iron status should be monitored during EPO treatment (**grade C recommendation; level IV evidence**).

Infections in Myeloma

- There must be 24 hour access to specialist advice for the patient and/or the primary care team (**grade C recommendation; level IV evidence**).
- Any febrile myeloma patient should be treated promptly with broad-spectrum antibiotics. Intravenous antibiotics are required for severe systemic infection. Aminoglycosides should be avoided, if possible (**grade C recommendation; level IV evidence**).
- Prophylactic trimethoprim-sulphamethoxazole may be given for the first 2 months in patients starting on 'standard' alkylating agent chemotherapy (**grade A recommendation; level Ib evidence**). They may also be used with other treatment regimens (**grade C recommendation; level IV evidence**).
- Vaccination against influenza, *Streptococcus pneumonia* and *Haemophilus influenza* is recommended but efficacy is not guaranteed (**grade B recommendation; level IIb evidence**).
- In patients with recurrent infections, prophylactic administration of immunoglobulins (0-4 g/kg body weight) may be helpful for patients in plateau phase (**grade A recommendation; level Ib evidence**) and other groups of myeloma patients (**grade C; level IV evidence**).

Other Complications

Neurological Complications

Cord compression

- Urgent MRI is the diagnostic procedure of choice to assess suspected cord compression in myeloma patients (**grade B recommendation; level IIB evidence**).
- If MRI is unavailable, impossible due to patient intolerance or contraindicated (e.g. intraorbital metallic foreign bodies or cardiac pacemakers) then an urgent CT scan should be performed (**grade B recommendation; level III evidence**).
- Dexamethasone should be commenced immediately – dosage in range of 8–16 mg/d (**grade C; level IV evidence**).
- Local radiotherapy is the treatment of choice and should be commenced within 24 hours of diagnosis (**grade C; level IV evidence**).
- Surgery is not indicated unless there is spinal instability (**grade C; level IV evidence**).

Peripheral neuropathy

- Review by a neurologist should be considered in any patient with myeloma or MGUS who has unexplained neuropathy (**grade C recommendation; level III evidence**).
- Neuropathy should be carefully assessed by clinical examination before starting any new therapy that may cause or exacerbate neuropathy. Close clinical monitoring should be undertaken during such therapy and treatment should be stopped or modified if necessary (**grade C recommendation; level III evidence**).

Initial Chemotherapy

- Vincristine, doxorubicin, and dexamethasone (VAD) or a VAD-type regimen should be used as initial therapy in patients where future high-dose therapy (HDT) is planned (**grade B recommendation; level II a evidence**).
- No firm recommendation can be made on whether oral idarubicin and dexamethasone or high-dose dexamethasone alone are equivalent to VAD.
- For older patients in whom HDT is not planned, either melphalan or cyclophosphamide should be used, with or without prednisolone (**grade A recommendation; level Ia evidence**).
- Thalidomide should only be used in newly diagnosed patients in the context of a clinical trial (**grade C recommendation; level IV evidence**).
- In all patients dose modifications may be required because of impaired renal function or cytopenia (**grade C recommendation; level IV evidence**).

Chemotherapy in Patients with Renal Failure

- For patients presenting in renal failure, either VAD or dexamethasone alone should be used (**grade B recommendation; level II b evidence**).
- Dexamethasone alone can be given as initial treatment pending decisions on subsequent chemotherapy and the outcome of full supportive measures (**grade C recommendation; level IV evidence**).
- Melphalan can be considered for patients with renal impairment in whom VAD or high-dose steroid-containing regimens are relatively contraindicated. The dose should be reduced by 25% in the first course if glomerular filtration rate (GFR) <30 ml/min and titrated against marrow toxicity in subsequent courses (**grade C recommendation; level IV evidence**).
- Thalidomide can be used without dose modification in patients with renal failure, but further data are needed before a firm recommendation can be made for its use.
- Younger patients with renal failure should be considered as possible candidates for future high-dose therapy (**grade B recommendation; level IIb evidence**).

Patients Refractory to Initial Therapy

- The most appropriate management must be determined on an individual basis depending on age, prior therapy and clinical condition (**grade C recommendation; level III evidence**).
- In younger patients with refractory disease that can be stabilised with second-line therapy and in whom a stem cell harvest can be achieved, high-dose melphalan is likely to offer the best prognosis (**grade B recommendation; level IIb evidence**)
- Where possible, the patient should be treated in the context of a clinical trial (**grade C recommendation; level III evidence**)

High-Dose Therapy and Transplantation

- HDT with autologous stem cell transplantation (ASCT) should be part of the primary treatment strategy in newly diagnosed patients up to the age of 65 years with adequate performance status and organ function (**grade A recommendation; level Ib evidence**).
- HDT with ASCT may be considered in patients aged >65 years with good performance status (**grade B recommendation; level IIa evidence**).

- Conditioning with melphalan alone, without total body irradiation (TBI), is recommended (**grade B recommendation; level IIa evidence**). The usual dose is 200 mg/m^2 but the dose should be reduced in older patients (over 65–70 years) and in renal failure.
- Planned double (tandem) ASCT cannot be recommended on the current evidence. However, it is recommended that enough stem cells are collected to support two high-dose procedures (**grade C recommendation; level IV evidence**).
- Currently available methods of purging have not demonstrated clinical benefit and are not, therefore, recommended (**grade A recommendation; level Ib evidence**).
- HDT and ASCT may be considered for patients with severe renal impairment (creatinine clearance/GFR <30 ml/min) but the dose of melphalan should be reduced to 140 mg/m^2 (**grade B recommendation; level IIb evidence**) and the procedure should only be carried out in a center with special expertise (**grade C recommendation; level IV evidence**).

Allogeneic Stem Cell Transplantation

- Patients up to the age of 50 years who have achieved at least a partial remission after initial therapy may be considered for HLA-matched sibling allogeneic stem cell transplantation (SCT). The procedure should be performed as part of a clinical trial, where possible (**grade B recommendation; level IIb evidence**).
- Donor lymphocyte infusions (DLI) should be considered for patients with persistent or progressive disease following transplantation (**grade B recommendation; level IIa evidence**).
- SCT should be carried out in European Group for Blood and Bone Marrow Transplantation-(EBMT) accredited centres where data are collected prospectively as part of international transplant registries (**grade C recommendation; level IV evidence**).
- Reduced-intensity conditioning (RIC) allografting may be considered in patients up to the age of 70 years with an HLA-matched sibling (**grade B recommendation; level IIb evidence**). The procedure would usually follow an initial autograft, should be done early in the disease phase and should always be done as part of a clinical trial (**grade C recommendation; level IV evidence**).
- Matched unrelated donor transplants using RIC may be considered within the context of a clinical trial. Conventional conditioning cannot presently be recommended (**grade C recommendation**).

Maintenance Therapies

- Interferon therapy may have some activity as maintenance therapy during plateau phase following conventional chemotherapy or following HDT (**level Ia evidence**) but an unfavourable cost per quality adjusted life year (QALY).
- No recommendation can be made regarding duration of interferon (IFN) treatment.
- Careful consideration should be given as to whether IFN should be continued in the face of side effects that impair quality of life (**grade C recommendation; level IV evidence**).

Management of Relapsed and Progressive Disease

- The most appropriate management must be determined on an individual basis depending on the timing of relapse, age, prior therapy, bone marrow function and other clinical circumstances (**grade C recommendation; level III evidence**).
- For the majority of patients who relapse after plateau or remission following melphalan and prednisolone (MP) as first line therapy the most appropriate chemotherapy is to restart oral melphalan ± prednisolone (**grade B recommendation; level III evidence**).
- Thalidomide should be considered in other patients (**grade B recommendation; level IIa evidence**). It is appropriate to start thalidomide alone and add dexamethasone if there is no evidence of response after 6–8 weeks (**grade C recommendation; level IV evidence**). No recommendation can be made on duration of therapy.
- Bortezomib is appropriate for third-line therapy in patients with reasonable performance status and organ function and reasonable life expectancy (**grade C recommendation; level III evidence**).
- Where possible, patients should be treated in the context of a clinical trial (**grade C; level III evidence**).
- Good supportive therapy is essential (**grade C recommendation; level III evidence**).

Management of Late-Stage Disease

- The primary aim at this stage is relief of symptoms (**grade C recommendation; level III evidence**).
- Good supportive care and continuity of care are essential (**grade C recommendation; level III evidence**).
- The palliative care team should be actively involved (**grade C recommendation; level III evidence**).
- The wishes of the patient and family should be actively sought (**grade C recommendation; level III evidence**).

Patient Information and Support

- The patient should be given the opportunity to be involved in treatment decisions at all times throughout the course of the disease (**grade C recommendation; level III evidence**).
- Written information should be provided where possible (**grade C recommendation; level III evidence**).
- Emotional and psychological support should be offered in a systematic fashion (**grade C recommendation; level III evidence**).

Definitions:

Levels of Evidence

Ia Evidence obtained from meta-analysis of randomised controlled trials

Ib Evidence obtained from at least one randomised controlled trial

IIa Evidence obtained from at least one well-designed, non-randomised study, including phase II trials and case–control studies

IIb Evidence obtained from at least one other type of well-designed, quasi-experimental study, (i.e. studies without planned intervention, including observational studies)

III Evidence obtained from well-designed, non-experimental descriptive studies. Evidence obtained from meta-analysis or randomised controlled trials or phase II studies which is published only in abstract form

IV Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Grades of Recommendations

Grade A, Evidence level Ia and Ib Recommendation based on at least one randomised controlled trial of good quality and consistency addressing specific recommendation

Grade B, Evidence levels IIa, IIb, and III Recommendation based on well-conducted studies but no randomised controlled trials on the topic of recommendation

Grade C, Evidence level IV Evidence from expert committee reports and/or clinical experiences of respected authorities

CLINICAL ALGORITHM(S)

A clinical algorithm is provided in the original guideline document, "Suggested treatment strategy for relapse."

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for most of the recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Accurate diagnosis and appropriate management of multiple myeloma, including control of disease and pain, prevention of debilitating and life-threatening complications, improved quality of life, and prolonged survival

POTENTIAL HARMS

Side effects of chemotherapy and conditioning therapy for stem cell transplantation, adverse events, treatment-related mortality

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Detailed chemotherapy protocols and dosages are not included; they are beyond the scope of this document. Provision of the detailed information and local protocols needed for the safe organisation, delivery and management of chemotherapy and related clinical care are the responsibility of each cancer centre/network (or equivalent in other countries). Statements appearing on drug dosage in the text mainly concern dosages used in specific trials or in the context of adjustment for renal impairment. The authors of these guidelines have made extensive efforts to ensure that treatments, drugs and dosage regimens are accurate. However, changes in information resulting from continuing research and clinical experience, reasonable differences in opinions among authorities, and the possibility of human error in preparation of the text require the clinician to exercise individual judgement when making a clinical decision. He/she must check product information and drug dosages before prescribing or administration.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

End of Life Care
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Smith A, Wisloff F, Samson D, UK Myeloma Forum, Nordic Myeloma Study Group, British Committee for Standards in Haematology. Guidelines on the diagnosis and management of multiple myeloma 2005. Br J Haematol 2006 Feb;132(4):410-51. [292 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Feb

GUIDELINE DEVELOPER(S)

British Committee for Standards in Haematology - Professional Association

SOURCE(S) OF FUNDING

British Committee for Standards in Haematology

GUIDELINE COMMITTEE

Guidelines Working Group of the UK Myeloma Forum (UKMF)

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the British Committee for Standards in Haematology Web site.

Print copies: Available from Dr Alastair G. Smith, Haematology Department, Southampton General Hospital, Tremona Road, Southampton SO61 6YD, UK. E-mail: alastair.smith@suht.swest.nhs.uk

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

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