Pan Birmingham NHS
Cancer Network

Guideline for the Management of Patients with Myeloma

Version History

Version	Summary of change	Date Issued
1.0	Endorsed by the Governance Committee	11.05.06
1.1	Following review by Guy Pratt	19.02.08
1.1	Re formatted (content not altered)	11.03.08
1.2	Reviewed by Mark Cook and Guy Pratt	19.03.08
1.3	Circulated to Haematology NSSG for final consultation – on hold re myeloma forum guidelines	14.04.08
1.4	With Guy Pratt's comments. Now likely to be consistent with Myeloma Forum Guidelines therefore for submission to September Clinical Governance. Circulated to Haematology NSSG for final approval	01.07.08
1.4	Formatting amendments	03.07.08
1.5	Following consultation	07.07.08
1.6	With comments from Zbigniew Rudzki. To be prepared for Clinical Governance.	13.08.08
1.7	With comments from Dr Milligan	20.04.09
1.8	With comments from Guy Pratt	05.05.09
1.9	With comments from Guy Pratt	26.10.09
2.0	Endorsed by the Clinical Governance Committee AS comment. AS comments incorporated.	17.03.10

Date Approved by Network Governance	**March 2010**

Date for Review	**March 2013**

1 Changes made during the review process in 2010/11

The Haematology NSSG has agreed to follow the British Committee for Standards in Haematology (BCSH) Guidelines on the diagnosis and management of multiple myeloma (2005). This has been updated in 2010 as two separate guidelines, one guideline for diagnosis and management and one guideline for supportive care. This is a network summary is not meant to be an exhaustive overview of myeloma management – please see references[4] for full version of these national guidelines.

2. This guidance has been produced to support the following:

a) The management of patients suspected of having Myeloma.
b) The management of patients diagnosed with Myeloma.

3. Guideline Background

3.1 In Pan Birmingham Cancer Network two hospitals are designated transplant centres for haematological malignancies - University Hospital Birmingham Foundation Trust and Heartlands Hospital (part of Heart of England Foundation Trust) These two hospitals treat patients with haematological malignancies at BCSH levels I-IV. In addition to this Good Hope Hospital (part of HEFT) practices to level 1 and Worcester Hospital and Sandwell and West Birmingham Hospitals NHS Trust, Sandwell site, practice to level 2.

3.2 Since version 1.0 of this guideline was issued (which itself shortly followed the UK MF/Nordic guidelines for the management of patients with myeloma) there have been significant advances in the care of myeloma patients. This document reflects the new national guidelines, published in 2010.

Guideline Statements

4. <u>Referral</u>

4.1 Patients with a combination of the following may have myeloma:
a) Symptoms of bone disease: typically persistent, unexplained backache.
b) Impaired renal function.
c) Anaemia.
d) Hypercalcaemia.
e) Recurrent or persistent bacterial infection.
f) Hyperviscosity.
g) Symptoms suggestive of spinal cord / nerve root compression.
h) Features suggestive of amyloidosis, such as nephrotic syndrome and cardiac failure.
i) Persistently raised ESR or plasma viscosity as an incidental finding.

4.2 Patients with any of the following should be referred **urgently** to the haematology team and seen within two weeks:
a) Bone pain associated with anaemia and raised ESR or plasma viscosity.
b) Bone X rays reported as being suggestive of myeloma.
c) Patients with an M-protein and either anaemia, hypercalcaemia or worsening renal impairment.
d) Patients with paraprotein found on routine testing and who have no clinical symptoms, anaemia, hypercalcaemia or renal impairment do not require urgent referral but should be discussed with the haematologist .

5. Investigation and Diagnosis

5.1 Patients suspected of having myeloma should undergo the following:

Screening tests (primary care)	**Tests to establish diagnosis**	**Tests to estimate tumour burden and prognosis**	**Tests to assess myeloma-related organ impairment (ROTI)**	**Special tests indicated in some patients**
FBC, ESR or plasma viscosity	Bone marrow aspirate and trephine biopsy	Trephine biopsy	FBC (anaemia)	Flow cytometry Vitamin B_{12} and folate assays*
Urea and electrolytes, calcium, albumin and uric acid Electrophoresis of serum and concentrated urine Quantification of non-isotypic immunoglobulins	Immunofixation of serum and urine Serum Free Light Chains.	Quantification of monoclonal protein in serum and urine Calcium Albumin *β*2-microglobulin	Urea and electrolytes, Creatinine clearance (measured or calculated) Calcium Albumin lactate dehydrogenase C-reactive protein Quantification of non- isotypic immunoglobulins	Renal Biopsy
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.				
*Where there is macrocytosis (not uncommon in myeloma).				

5.2 The marrow slides should be reported by a haematopathologist (histologist or haematologist) trained in myeloma morphology. They should be reviewed by the core MDT members at the next available MDT meeting.

6. Treatment

6.1 All patients:

Local, Network and BCSH guidelines should be followed for the management of the following treatments and care:

a) Blood and blood product support.
b) The use of growth factors.
c) Neutropenia – prevention and treatment.

6.2 Supportive Care

A proactive approach should be taken in the detection and management of problems associated with the diagnosis of myeloma. The more common ones include pain, renal impairment, anaemia and infections. Less commonly patients may experience cord compression, peripheral neuropathy, hyperviscosity, bleeding and AL amyloidosis. As myeloma is currently incurable and is life limiting, good supportive care is essential to maintain a good quality of life.

6.3 Thromboprophylaxis

For patients receiving treatments with an associated increased risk of venous thromboembolism (VTE), e.g. thalidomide and Lenalidomide, thromboprophylaxis should be offered. Treatment options include low molecular weight heparin, aspirin or formal anticoagulation with warfarin, see below. Low dose warfarin should not be offered. **Recommendations (as per BCSH 2010 guidelines) are below:**

a) Cancer, cancer therapies, infection, previous VTE, immobility, obesity, paraplegia, ESA treatment, dehydration and renal failure are all well-recognised risk factors for venous thromboembolism (VTE), particularly in hospitalised patients. As with other areas of thromboprophylaxis, a risk stratified approach is appropriate in patients with myeloma (Grade C recommendation; level IV evidence).
b) All patients who are due to start thalidomide or lenalidomide-containing therapy should undergo a risk assessment for VTE and prospectively receive appropriate thromboprophylactic measures. In patients receiving thalidomide or lenalidomide (Grade C recommendation; level IV evidence):
c) If no other VTE risk factors are present, aspirin 75-150 mg o.d. may be considered as VTE prophylaxis unless contraindicated (Grade C recommendation; level IV evidence).
d) If one or more major risk factors for VTE are present, prophylaxis with LMWH or adjusted therapeutic-dose warfarin is appropriate. This should be the consideration in most patients with active myeloma undergoing treatment with combination chemotherapy, unless contraindicated (Grade C recommendation; level IV evidence).
e) Patients with previous VTE should be considered for prophylaxis with adjusted therapeutic-dose warfarin or LMWH (high risk prophylactic dose should be considered). There is no role for fixed, low dose warfarin (Grade C recommendation; level IV evidence).

f) The duration of thromboprophylaxis remains unclear but guided by risk factors such as active disease (e.g. for the first 4 to 6 months of treatment until disease control achieved) and de-escalated or discontinued unless there are ongoing significant risk factors (Grade C recommendation; level IV evidence).
g) Treatment of confirmed VTE should follow current practice guidelines using adjusted dose warfarin or LMWH and appropriate monitoring (Grade C recommendation; level IV evidence).

6.4 Access to the following is mandatory:-

a) Specialist palliative care support.
b) Specialist radiation oncology support.
c) Specialist orthopaedic Support.
d) Specialist neurosurgical/spinal surgery support.
e) Specialist support capable of providing vertebroplasty/balloon kyphoplasty.

6.5 Bisphosphonate therapy

Recommendations - bisphosphonates (as per BCSH guidelines) are below:

a) Bisphosphonate therapy is recommended for all patients with symptomatic multiple myeloma, whether or not bone lesions are evident (grade A; level 1b)
b) Zoledronic acid and pamidronate both show efficacy with respect to SRE prevention (grade A; level 1b) but early data regarding prolongation of EFS and OS in a large randomised trial suggest that zoledronic acid should be the bisphosphonate of choice.
c) Sodium clodronate is less effective than zoledronic acid but has a significantly lower incidence of BONJ (grade A; level 1b)
d) There is no consensus regarding the duration of bisphosphonate therapy.
e) All patients to be started on long term bisphosphonate treatment should be warned of the risk of BONJ and its predisposing factors (Grade C recommendation; level IV evidence).
f) All patients to be started on IV BP should be referred for a dental opinion and any teeth of poor prognosis extracted before initiation of BP therapy. Patients on long-term oral bisphosphonates should have regular dental care and maintain excellent oral hygiene (Grade C recommendation; level IV evidence).
g) Invasive dental procedures in patients on IV or long-term oral bisphosphonate should be avoided as far as possible. For patients on IV BP, a specialist opinion should be sought prior to any extractions (Grade C recommendation; level IV evidence).
h) Patients with suspected BONJ should be referred to a clinician with special interest and expertise in the management of this condition (Grade C recommendation; level IV evidence).

6.6 Initial Chemotherapy

Basic principles:

a) Where possible, all patients should be entered into a relevant clinic trial. Myeloma XI is the current national trial which opened in 2010.

b) Where possible, therapy should be individualised to the wishes, needs and fitness of the patient
c) Treatments are currently grouped whether a patient is suitable for intensive (i.e. is fit enough for high dose therapy) or non intensive (is not fit for high dose therapy either through performance status or age).

6.7 Intensive Treatment

a) There is sufficient published and unpublished evidence to recommend a Thalidomide based combination as first line treatment. The current UK standard is Cyclophosphamide/Thalidomide/Dexamethasone (CTD) and should be given for a minimum of four cycles.
b) There is evidence that combination therapies using other novel drugs such as Bortezomib and Lenalidomide have significant efficacy in this setting. However, these drugs are neither licensed nor NICE approved for this indication and therefore are not recommended at present outside a clinical trial.
c) High dose therapy and autologous stem cell transplant (ASCT) is now considered a standard component of the primary treatment strategy in newly diagnosed patients under the age of 65 with adequate performance status and organ function. Patients between the ages of 65-70 should be considered on an individual basis.
d) Recommended conditioning for the transplant is with melphalan alone, without TBI.
e) Alternative conditioning should only be considered as part of a clinical trial.
f) Planned double (tandem) ASCT is not recommended, however, enough stem cells to support two procedures should be collected where possible.
g) Purging is not recommended.
h) Patients with renal impairment should be considered for transplant with reduced dose melphalan.

6.8 Non intensive therapy.

a) Patients should be considered for non intensive therapy when high dose therapy is considered inappropriate because of performance status or age.
b) There is now sufficient randomised control trial data to recommend a Thalidomide combination as primary therapy. The current published regimen is Melphalan/Prednisolone/Thalidomide (MPT). Unpublished data suggests that the 'UK Standard' attenuated Cyclophosphamide/Thalidomide/Dexamethasone (CTD a) is as effective. The aim is to give a minimum of six cycles and to continue until maximal response/plateau is achieved but treatment needs to be tailored to performance status and tolerance.
c) In patients intolerant of, or not wishing to take, Thalidomide treatment with either Melphalan or Cyclophosphamide, these agents without thalidomide should be used. Melphalan is conventionally used in association with Prednisolone (MP) although there is little data to support this.
d) There is evidence that combination therapies using other novel drugs such as Bortezomib and Lenalidomide have significant efficacy in this setting. However, these drugs are neither licensed nor NICE approved for this indication and therefore are not recommended at present outside a clinical trial.
e) Appropriate dose modifications should be made in the context of renal impairment or cytopenias (see UKMF/Nordic guidelines 2005).

6.9 Renal Impairment

Up to 20% of patients with multiple myeloma will present with renal impairment. Approximately 10% of patients will require dialysis. Renal failure is associated with a high mortality in multiple myeloma patients and therefore supportive care is paramount, particularly in the first 60 days after diagnosis.

a) Reversible causes of renal impairment should be identified and treated (these include dehydration, hypercalcaemia, sepsis and drugs such as NSAIDs).
b) For patients with persisting renal impairment, a renal opinion should be sought at an early stage.
c) Where the cause of renal impairment is unclear, a renal biopsy should be considered.
d) Patients can be safely treated with a Thalidomide combination (Thalidomide/Dexamethasone). Careful monitoring should be carried out for hyperkalaemia.
e) Other novel agents (Bortezomib and Lenalidomide) have been used successfully in patients with renal failure but are not licensed or NICE approved for this indication and therefore cannot be recommended outside a clinical trial.
f) Renal failure is not a barrier to progression to high dose therapy. In patients with no other contraindication, high dose therapy should therefore be offered.

6.10 Refractory Disease

a) Where possible patients should be entered into a relevant clinical trial.
b) Response criteria and definitions are attached in Table 1.
b) Patients with refractory disease should be offered treatment on an individual basis depending on age, prior therapy and clinical condition.
c) Younger patients whose disease can be stabilised with second line therapy should be considered for an autologous transplant.
d) Where the patient has not received Thalidomide as first line therapy, a Thalidomide combination should be considered as second line therapy. Other novel agents (Lenalidomide and Bortezomib) have been demonstrated to have some efficacy in this setting, but are not licensed or NICE approved and therefore cannot be recommended outside a clinic trial.

6.11 Allogeneic Transplant

a) Patients with an ISS score of 2 or 3 up to the age of 50 years and who have achieved at least a VGPR or CR after initial therapy may be considered for HLA-matched sibling allogeneic stem cell transplant, as part of a clinical trial where possible.
b) Reduced intensity conditioning (RIC) allografting should only be considered in patients up to the age of 70 years with an HLA-matched sibling as part of a clinical trial.
c) Matched unrelated donor transplants using RIC should only be considered as part of a clinical trial.
d) Donor lymphocyte infusions (DLI) should be considered for patients with persistent or progressive disease following allogeneic transplantation.
e) As patients with an ISS score of 1 have a medial survival of 110 months following autologous transplant, allogeneic transplant cannot be routinely recommended for this group of patients.

6.12 Maintenance Therapies

a) Interferon is not recommended as a maintenance therapy.
b) There is insufficient data to recommend lenalidomide or bortezomib in this setting except as part of a clinical trial.
c) There is evidence for patients not achieving a VGPR after high dose therapy that Thalidomide may improve response when given as a maintenance treatment. Because of the concern over resistant relapse, consideration should be given to stopping thalidomide treatment after 6-12 months although further study data is required to clarify this.

6.13 Management of Relapsed / Progressive disease (See appendix 1 for definitions).

a) Care in these circumstances should be managed on an individual basis.
b) Where possible patients should be managed in the context of a clinical trial.
c) Good supportive therapy is essential.
d) Bortezomib is approved by NICE for use in patients at first relapse who have had or are unfit for a transplant. It should therefore be offered as treatment to patients at first relapse who fit the NICE criteria. Management of the patients should be in accordance with the NICE guidance and compliant with the 'Velcade Reimbursement Scheme'.
e) Patients with relapsed disease may be treated with thalidomide combination regimens such as CTD or thalidomide/dexamethasone. Alkylating agents with or without steroids are appropriate for patients intolerant of thalidomide regimens, ineligible for velcade or lenalidomide or with prolonged responses to previous alkylating agents.
f) Lenalidomide is licenced for use at first relapse and approved by NICE for relapsed patients who have received two or more previous therapies. It should therefore be offered to patients at second or subsequent relapse who fit the NICE criteria and should be used in accordance with the NICE guidance.

7. Follow-up

7.1 Follow-up should be as per trial requirements or in the haematology clinics at 3 - 4 months when in plateau phase. Patients should be advised to report promptly to their G.P. team if they develop any signs or symptoms that might indicate disease relapse or progression. Rapid access to the haematology clinic (within 2 weeks) is essential for suspected relapse.

8. Palliative Care

8.1 Early links should be made to the palliative care team where the treatment intent is not curative or where the patient has symptoms that are difficult to manage.

Monitoring of the Guideline

Implementation of the guidance will be considered as a topic for audit by the NSSG in 2013.

References

1 BCSH 2005 Guidelines on the diagnosis and management of multiple myeloma 2005 (UKMF/Nordic). www.bcshguidelines.com

2 NICE 2005 Referral Guidelines for Suspected Cancer www.nice.org.uk

3 NICE 2007 Bortezomib Monotherapy for Multiple Myeloma http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11869

4 BCSH 2010 Guidelines on the diagnosis and management of multiple myeloma. www.bcshguidelines.com

5 BCSH 2010 Guidelines on supportive care in Myeloma. www.bcshguidelines.com

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Appendix 1

From Durie B et al (Leukemia 2006)

Table 1: Response Criteria

Table 5 International Myeloma Working Group uniform response criteria: CR and other response categories

Response subcategory	*Response criteria*[a]
sCR	CR as defined below plus Normal FLC ratio and Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[c]
CR	Negative immunofixation on the serum and urine and Disappearance of any soft tissue plasmacytomas and $\leqslant$5% plasma cells in bone marrow[b]
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level $<$100 mg per 24 h
PR	$\geqslant$50% reduction of serum M-protein and reduction in 24-h urinary M-protein by $\geqslant$90% or to $<$200 mg per 24 h If the serum and urine M-protein are unmeasurable,[d] a $\geqslant$50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, $\geqslant$50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was $\geqslant$30% In addition to the above listed criteria, if present at baseline, a $\geqslant$50% reduction in the size of soft tissue plasmacytomas is also required
SD (not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates)	Not meeting criteria for CR, VGPR, PR or progressive disease

Abbreviations: CR, complete response; FLC, free light chain; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response.
[a]All response categories require two consecutive assessments made at anytime before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.
[b]Confirmation with repeat bone marrow biopsy not needed.
[c]Presence/absence of clonal cells is based upon the k/λ ratio. An abnormal k/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/λ of $>$4:1 or $<$1:2.
[d]Refer to Table 4 for definitions of measurable disease.

From Durie B et al (Leukemia 2006)

Table 2 Progression and relapse

Table 6 International Myeloma Working Group uniform response criteria: disease progression and relapse

Relapse subcategory	*Relapse criteria*
Progressive disease[a] To be used for calculation of time to progression and progression-free survival end points for all patients including those in CR (includes primary progressive disease and disease progression on or off therapy)	Progressive Disease: requires any one or more of the following: Increase of ⩾25% from baseline in Serum M-component and/or (the absolute increase must be ⩾0.5 g/dl)[b] Urine M-component and/or (the absolute increase must be ⩾200 mg/24 h Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be >10 mg/dl. Bone marrow plasma cell percentage: the absolute % must be ⩾10%[c] Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia (corrected serum calcium > 11.5 mg/dl or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder
Clinical relapse[a]	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features)[b] It is not used in calculation of time to progression or progression-free survival but is listed here as as something that can be reported optionally or for use in clinical practice 1. Development of new soft tissue plasmacytomas or bone lesions 2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion 3. Hypercalcemia (>11.5 mg/dl) [2.65 mmol/l] 4. Decrease in hemoglobin of ⩾2 g/dl [1.25 mmol/l] (see Table 3 for further details) 5. Rise in serum creatinine by 2 mg/dl or more [177 μmol/l or more]
Relapse from CR[a](To be used only if the end point studied is DFS)[d]	Any one or more of the following: Reappearance of serum or urine M-protein by immunofixation or electrophoresis Development of ⩾5% plasma cells in the bone marrow[c] Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia see below)

Abbreviations: CR, complete response; DFS, disease-free survival.
[a]All relapse categories require two consecutive assessments made at anytime before classification as relapse or disease progression and/or the institution of any new therapy.
[b]For progressive disease, serum M-component increases of ⩾1 gm/dl are sufficient to define relapse if starting M-component is ⩾5 g/dl.
[c]Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.
[d]For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

Approval Date of Network Site Specific Group Date 17.03.10

Approval Date by the Clinical Governance Team Date 17.03.10

Approval Signatures

Pan Birmingham Cancer Network Governance Committee

Name: Doug Wulff

Signature Date 17.03.10

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To be reviewed by the NSSG in March 2013