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# Pan-London Haemato-Oncology Clinical Guidelines

## Plasma Cell Disorders

January 2020

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## Disclaimer

These guidelines should be read in conjunction with the latest NICE guidance, and all applicable national/international guidance. The prescribing information in these guidelines is for health professionals only. It is not intended to replace consultation with the Haematology Consultant at the patient's specialist centre. For information on cautions, contra-indications and side effects, refer to the up-to-date prescribing information. While great care has been taken to see that the information in these guidelines is accurate, the user is advised to check the doses and regimens carefully and if there is any uncertainty about the guidance provided, you should discuss your queries with a Haematology Consultant or Senior Pharmacist. No set of guidelines can cover all variations required for specific patient circumstances. It is the responsibility of the healthcare practitioners using them to adapt them for safe use within their institutions and for the individual needs of patients.

## Contact us

The writing cycle for the guidelines will be from May-July each year. If you wish to be part of the writing group, please contact us through the following link: [Pan London Blood Cancer](#) (or via [uclh.panlondonbloodcancer@nhs.net](mailto:uclh.panlondonbloodcancer@nhs.net)).

If you wish to report errors or omissions that require urgent attention please contact us via the same email addresses.

# 1 Introduction

The plasma cell disorders are a group of related diseases that result from a clonal proliferation of plasma cells. They are usually typified by the presence in the serum or urine of a monoclonal protein (M-protein) which can be either a complete molecule (paraprotein) or light chains (Bence Jones protein), or both. While each disorder has a distinct diagnostic and clinical phenotype, there is a large degree of overlap between them and hence they are often investigated and clinically managed together. This group of disorders includes multiple myeloma, monoclonal gammopathy of undetermined significance (MGUS), primary amyloidosis, solitary plasmacytoma and POEMS syndrome.

The British Committee for Standards in Haematology (BCSH) in collaboration with the UKMF have issued comprehensive guidelines on the investigation, diagnosis, clinical management and supportive care of multiple myeloma (MM),<sup>1–3</sup> MGUS,<sup>1</sup> plasmacytoma<sup>4</sup> and AL amyloidosis<sup>5, 6</sup>. These guidelines are based on the BCSH/UKMF guidelines and International Myeloma Working Group (IMWG) consensus guidelines updated to include relevant additional evidence where appropriate.

## 1.1 Multiple myeloma

Multiple myeloma (MM) is the second most common haematological malignancy and is characterised by the proliferation of clonal plasma cells in the bone marrow. It is divided into several distinct clinical phases.

The first is a pre-malignant stage termed MGUS in which there is a population of clonal plasma cells that produce a monoclonal protein; however, patients are asymptomatic but there is a risk of progressing from MGUS to myeloma. The next stage is termed asymptomatic myeloma/smouldering myeloma. It has a higher percentage of plasma cells in the bone marrow but still does not cause end organ damage and mostly does not require treatment apart from in high risk patients. Myeloma requiring treatment, in contrast, causes detectable damage to the bones or kidneys and/or suppression of normal bone marrow function. Plasma cell leukaemia is the most aggressive stage of the disease and is characterised by the presence of plasma cells in the peripheral blood.

Myeloma is the 17th most common cancer in the UK and accounts for approximately 1% of all cancers.<sup>7</sup> It has a UK age-standardised incidence of 5.4 per 100,000 persons but is predominantly a disease of those aged over 60 years and, as such, the incidence is increasing as the population ages. There are currently approximately 5,500 new cases diagnosed each year in the UK. Epidemiological studies have established increasing age, male gender (60:40), familial background and a past history of MGUS as being risk factors for MM. It has been suggested that myeloma is always preceded by MGUS; however, only 1% of patients with MGUS will progress to MM per year. It has also been observed that there is a 1.5–3-fold increased incidence in people of black African/Caribbean origin with a younger age of onset.

Significant advances have been made in the treatment of myeloma with the introduction of several new and effective drugs in the past decade. These include thalidomide, its analogue lenalidomide, and the proteasome inhibitor bortezomib. While these new drugs have undoubtedly improved the outcome of patients with myeloma, with recent epidemiologic studies demonstrating survival improvements over the past decade,<sup>7, 8</sup> the disease still remains incurable. Sustained improvement in the outcome and eventual cure requires the development of new therapies based on better understanding of the disease biology. In fact, improved versions of the current drugs as well as

several new classes of drugs are currently undergoing evaluation, and many of them appear very promising based on initial results.

The following are clinical variants of myeloma:

### 1.1.1 Smouldering/asymptomatic myeloma

This is a disorder with diagnostic features consistent with myeloma by virtue of monoclonal protein level or bone marrow plasma cell infiltration but without myeloma-related organ or tissue injury, thereby usually not requiring myeloma-directed therapy. The rate of transformation from asymptomatic to treatment-requiring symptomatic myeloma is higher than for MGUS. International Myeloma Working Group guidelines recommend initiating myeloma systemic anti-cancer treatment (SACT) for those patients with smouldering disease at highest risk for early progression.<sup>9</sup>

### 1.1.2 Plasma cell leukaemia

This is an aggressive subgroup of myeloma with the presence of peripheral blood plasma cells either arising de novo (primary) or from an existing case of myeloma (secondary). Primary plasma cell leukaemia has a distinct phenotype occurring in 2–4% of new myeloma patients and is typified by its aggressive clinical course.

## 1.2 Monoclonal gammopathy of undetermined significance (MGUS)

MGUS is one of the most common pre-malignant disorders and affects approximately 3.5% of the population older than 50 years. IgG, IgA and IgM MGUS are defined by an M-protein <30g/L, bone marrow plasma cell percentage <10% (lymphoplasmacytoid lymphocytes <10% in the case of IgM), and the absence of signs or symptoms related to MM or other lymphoproliferative malignancies such as Waldenström's macroglobulinemia (WM), immunoglobulin light chain (AL) amyloidosis, chronic lymphocytic leukaemia (CLL), or B-cell lymphoma.

There is an average risk of progression to MM or, to a lesser extent, other lymphoproliferative disorders of 1% per year. Typically, patients with IgG or IgA MGUS progress to MM, and patients with IgM MGUS progress to WM or other lymphoproliferative disorders. Light chain MGUS is the precursor of light chain MM, and is defined by an abnormal  $\kappa/\lambda$  serum free light chain (SFLC) ratio, increase in concentration of the involved light chain, and absence of expression of a monoclonal peak of immunoglobulin heavy chain in the serum on immunofixation.<sup>1</sup> In contrast, in renal disease and in the case of polyclonal B-cell activation there may be increased levels of both  $\kappa$  and  $\lambda$  chains, but with a normal ratio. Light chain MGUS has a prevalence of ~0.7–0.8% in persons aged 50 years and older.

While most patients with MGUS will have no clinical symptoms, a small number can be associated with peripheral neuropathy (MGAN), bleeding abnormalities or skin lesions. Increasingly, a subset of patients with renal impairment as a result of a range of paraprotein-related renal lesions is being recognised and labelled as monoclonal gammopathy of renal significance (MGRS).<sup>10</sup>

## 1.3 Solitary plasmacytoma

This can be considered as a tumour composed of plasma cells. Most commonly it occurs in patients with underlying myeloma; however, it can also occur in isolation either singly or as multiple plasma cell tumours.

Solitary plasmacytoma of the bone (SBP) is a single, often destructive, collection of clonal plasma cells that occurs in bone without other evidence of myeloma. It is rare, occurring almost twice as

often in men with a median age at diagnosis of 60 years. The commonest site at diagnosis is the axial skeleton. Up to 75% of patients will have a monoclonal protein detectable in the blood or urine. More than 50% of patients will subsequently develop myeloma.

Extramedullary plasmacytoma (EP) are less common than SBP and are the result of a soft tissue accumulation of clonal plasma cells. Over 80% occur in the head and neck. Fewer than 25% of patients will have an associated monoclonal protein detectable and, following appropriate therapy, the subsequent development of myeloma is uncommon.

## 1.4 POEMS syndrome

This is a rare plasma cell proliferative syndrome which combines polyneuropathy, a monoclonal protein with a wide range of other organ or tissue abnormalities. It can be associated with MGUS, myeloma and with other plasma cell proliferative conditions such as Castleman's disease.<sup>11</sup>

## 1.5 AL amyloidosis

This occurs as the result of tissue deposition of protein fibrils derived from circulating monoclonal light chains and may lead to end organ damage. Deposition can occur throughout the body but typically renal, liver and cardiac involvement is clinically dominant. It is a rare condition but may complicate up to 15% of myeloma cases. It also arises de novo as primary AL amyloidosis with an incidence of 8–10 per million persons with a median age at diagnosis of 63 years.

## 1.6 Light chain deposition disease, monoclonal immunoglobulin deposition disease (MIDD) and monoclonal gammopathy of renal significance

These rare disorders are characterised by the deposition of light chains or intact monoclonal immunoglobulin deposition in a range of organs. In MIDD, the kidney is most commonly affected; however, deposits can also occur in the heart and liver. These disorders can occur both in association with myeloma as well as a discrete problem. Monoclonal gammopathy of renal significance is a recently described entity where patients with low grade bone marrow clonal disorder develop a diverse range of renal problems from glomerulopathy, tubular disease and tubule-interstitial diseases. The key diagnosis is based on renal histology and needs specialist referral.



## 2 Early Diagnosis and Prevention

Myeloma often presents late due to a failure to recognise symptoms. Patients with persistent bone pain for longer than 4–6 weeks with no obvious trigger should have an FBC, U+E, and calcium, serum protein electrophoresis and urine protein electrophoresis ray as a minimum with appropriate imaging dictated by symptoms also being a consideration. Further warning signs/symptoms would include neuropathic symptoms, history of bone pain elsewhere, recurrent infections and lethargy. Unexplained abnormalities in the above investigations should trigger an urgent referral to haematology via the 2 week wait pathway.

*All labs that perform serum electrophoresis and immunoglobulin profiles as well as serum free light chain assays should have agreed procedures for urgently notifying the local haematologist if an unexpected/unknown abnormal electrophoretic result or serum free light chain result is flagged.*

### 2.1 Referral pathways from primary care

Patients with suspected plasma cell disorder should be referred to a haematologist for assessment. It is suggested for patients with a high paraprotein (over 15 g/L) / light chains (over 500mg/L), significant anaemia, hypercalcaemia, bone lesions or renal failure to be referred as an emergency or via the 2 week wait pathway as clinically indicated.

All new patients should be referred to the multidisciplinary team (MDT) for confirmation of diagnosis, prognosis and management plan, taking into account their performance status, needs and co-morbidities. Patients requiring urgent treatment may start prior to a formal MDT discussion (as per local practice). The workings of the MDT are defined in the NICE publication (NG35 Feb 2016).

All cases with high risk disease should be identified, discussed frequently and early with the myeloma team at a tertiary centre.

All patients with a new diagnosis of a plasma cell disorder (including monoclonal gammopathy with clinical sequelae) should be discussed at a plasma cell disorder MDT to review investigations, confirm the diagnosis, register the case and plan clinical management.

Post-treatment outcomes will also be discussed in the MDT/myeloma team as needed to allow review of clinical decisions made. The MDT/myeloma team will review disease progress and relapse and subsequent treatment decisions.

All cases destined for autologous stem cell transplantation (ASCT) should be referred to a JACIE accredited transplant centre.

Some MDTs hold a separate myeloma meeting and others discuss patients with myeloma as part of their haematology MDT.

Information to be captured and documented prior to or during the MDT should include:

- demographic information
- names of referring physician and GP
- performance status (Eastern Cooperative Oncology Group/ECOG)

- an indicator of co-morbidities such as cardiac disease, diabetes, pre-existing renal disease, respiratory disease
- any relevant history
- pertinent positive and negative findings on physical examination (splenomegaly, rashes, etc)
- full blood count (FBC), haematinics, liver function tests (LFTs), urea and electrolytes (U&E), lactate dehydrogenase (LDH), urate, beta-2 microglobulin (B2M), C-reactive protein (CRP), albumin count, direct antiglobulin test (DAT), vitamin D, B12, coagulation screen and serum protein electrophoresis (SPEP) and serum free light chains; urine for Bence Jones protein or total urine protein, protein/creatinine ratio
- NT pro BNP and troponin-T/I (in cases of suspected amyloid)
- bone marrow aspirate and trephine histology
- bone marrow aspirate immunophenotyping, if relevant
- interphase FISH
- specific diagnosis/category of plasma cell disorder
- relevant imaging
- risk score (at least International Staging System/ISS)
- availability of a clinical trial/research study, if the patient is eligible
- management and treatment plan
- clinical nurse specialist (CNS)/key worker
- named consultant /treating team.

The MDT outcome form should be sent to the GP within 24 hours of MDT discussion.

### 3 Investigation and Diagnosis

Myeloma often presents late due to a failure to recognise symptoms. Patients with persistent bone pain for longer than 4–6 weeks with no obvious trigger should have a FBC, U+E, and calcium, serum protein electrophoresis and urine protein electrophoresis ray as a minimum with appropriate imaging dictated by symptoms also being a consideration. Further warning signs/symptoms include neuropathic symptoms, history of bone pain elsewhere, recurrent infections and lethargy. Unexplained abnormalities in the above investigations should trigger an urgent referral to haematology using the 2 week wait form.

#### 3.1 Investigations and assessments required to ensure full diagnosis with prognostic information

##### 3.1.1 Full presenting history should be taken and examination performed, with specific reference to:

- bone pain, or concerning unexplained pains
- fatigue
- fever, sweats
- recurrent infections
- symptoms of hypercalcaemia
- anaemia
- neuropathy
- gastro-intestinal disturbance and weight loss
- organomegaly
- skin changes
- medical co-morbidities
- family history
- performance status (Eastern Cooperative Oncology Group/ECOG is preferred).

##### 3.1.2 Peripheral blood tests with a suspected and/or confirmed plasma cell disorder that should be carried out include:

As listed in section above.

##### 3.1.3 Urinalysis

- All patients should be screened for urinary Bence Jones protein and excess urine albumin loss
- Urine electrophoresis (Bence Jones protein) including immunofixation and quantitation (24-hour urine as indicated), or urine protein/creatinine ratio
- Urinary protein or urinary protein: creatinine ratio (as per local practice)
- Creatinine clearance.

### 3.1.4 Bone marrow examination is indicated for patients with:

- A suspicion of myeloma based on presence of paraprotein, elevated serum free light chains particularly when associated with:
  - anaemia
  - renal impairment
  - hypercalcaemia
  - immunoparesis
  - lytic bone lesions or >1 focal lesion on whole body imaging
  - recurrent infection
- Light chain deposition disease or amyloid deposition.

Samples to be taken:

- bone marrow aspirate
  - morphological assessment/plasma cell enumeration
  - cytogenetics/fluorescence in hybridisation (FISH)
  - flow cytometry (as available) (always needed in AL amyloidosis, MIDD and MGRS)
  - molecular or tissue banking (as available)
- bone marrow trephine (minimum 20mm)
  - immunohistochemistry to determine extent of plasma cell infiltration.

### 3.1.5 Biopsy of abnormal lesions

- Some cases of myeloma present with abnormal masses, collapsed vertebrae or pathological fractures. In this situation, a biopsy of the lesion is recommended.

## 3.2 Clinically relevant prognostically important results that should be documented

The following clinically relevant prognostically important results should be documented:

- age
- performance status (ECOG)
- beta-2 microglobulin
- albumin
- creatinine
- Ca
- LDH
- CRP
- percentage and morphology of bone marrow plasma cells (i.e. blastic or otherwise)
- adverse cytogenetic/FISH abnormalities:
  - t(4;14)

- t(14;16)
- t(14;20)
- 17p-
- 1p- (in transplant eligible patients only)
- 1q+
- Gene mutation panel if available (NHS Genomics list includes *TP53*, *NRAS*, *KRAS*, *BRAF*, *FAM46C*, *DIS3*)

### 3.3 Imaging investigations

Imaging plays an important role in the assessment of multiple myeloma. The accurate delineation of bone disease (focal and/or diffuse) which can involve any part of the skeleton, informs on prognosis, and contributes to risk stratification and clinical management.<sup>12, 13</sup> Significant advances in imaging technologies have paralleled developments in therapy for myeloma. Local availability will determine the imaging investigation undertaken.

NICE have issued guidelines for those with **newly** diagnosed myeloma (NICE, NG35, Feb 2016). In addition, IMWG have issued imaging guideline in 2019<sup>46</sup>. Important issues that need highlighting:

- Those with an established diagnosis of myeloma should have whole body imaging. The choice of what is used will depend upon local availability. Clinicians can choose between whole body (wb) MRI, PET-CT or low dose whole body CT. NICE have suggested MRI in preference to the other modalities. The advantage of wbMRI and PET/CT is that they provide functional assessment of myeloma that can be used to monitor response to therapy. Whilst the IMWG suggests PET/CT as the modality of choice (Cavo *et al.*, *Lancet*, Oncology, Apr 2017), there is insufficient data when comparing diffusion weighted wbMRI to PET/CT.
- Patients with non-secretory/oligosecretory myeloma should have wbMRI or PET/CT as this will allow assessment of response to treatment, due to the lack of a measurable biochemical marker.
- When functional imaging is employed (wbMRI or PET/CT) these should be repeated at the end of induction therapy to provide an additional assessment of response. It is important for this data to be collected prospectively. These modalities should also be used in the relapsed setting.
- Skeletal surveys should **not** be routinely used due to their poor sensitivity at detecting osteolytic disease, compared with the other modalities listed above. Whole body imaging should be employed.
- Limited MRI spine or pelvis should be performed in those with suspected cord compression or other nerve impingement. If MRI cannot be performed then a CT should be used.
- Patients should be entered into clinical studies assessing these imaging modalities.

NICE issued guidelines for those with **suspected** myeloma (NICE, NG35, Feb 2016). Important issues that need highlighting and differentiating from those with established myeloma:

- Those with a likely diagnosis of myeloma (likely CRAB-related symptoms, or a high level of paraprotein) should have whole body imaging. Whilst NICE suggests wbMRI, any of the whole body imaging modalities can be used.

- For those who are likely to have a benign gammopathy, there is no need to perform any imaging in the absence of symptoms. Where there are potentially concerning symptoms in these patients (e.g. localised back pain), directed imaging should be performed rather than whole body imaging. This may include plain X-rays, or CT/MRI as appropriate. There is no need to perform skeletal surveys in any of these patients.
- Bone scanning has no place in the staging of patients with myeloma.

IMWG issued guidance for imaging of patients with solitary plasmacytoma:

- PET/CT is recommended as initial imaging for solitary extramedullary plasmacytoma.
- wbMRI is recommended as initial imaging of solitary bone plasmacytoma.
- Yearly surveillance imaging with whichever scan is performed at diagnosis is recommended for at least 5 years.

IMWG issued guidance for ongoing imaging of patients with an established diagnosis of asymptomatic myeloma:

- Yearly whole body imaging (ideally wbMRI if available) is recommended for at least 5 years in patients with newly diagnosed asymptomatic myeloma.

### 3.4 Other investigations for specific subtypes of disease

#### 3.4.1 For amyloidosis:

- molecular characterisation of amyloid subtype on tissue biopsy by DNA analysis/fibril sequencing at National Amyloid Centre, Royal Free Hospital, London (NAC, RFH)
- electrocardiograph (ECG), echocardiogram and/or cardiac MRI, NT-pro-BNP, troponin T (for amyloid staging)
- renal/liver ultrasound, if clinical suspicion
- bone imaging to rule out myeloma
- serum amyloid P (SAP) scan (at NAC, RFH)
- upper and lower gastrointestinal assessment by endoscopy, if clinically indicated
- nerve conduction studies and autonomic function tests, if clinically indicated
- <sup>99m</sup>Tc-DPD scan in older patients (>65 years) to exclude ATTR amyloidosis (available at Royal Free and Barts).

#### 3.4.2 For suspected POEMS syndrome:

- testosterone, oestradiol
- fasting glucose, glycosylated haemoglobin
- thyroid stimulating hormone (TSH), parathyroid hormone (PTH), prolactin, cortisol
- luteinising hormone (LH), follicle-stimulating hormone (FSH), adrenocorticotrophic hormone (ACTH)
- ultrasound or CT abdomen to determine organomegaly

- vascular endothelial growth factor (VEGF) levels
- lung function
- nerve conduction studies
- imaging for evidence of osteosclerotic lesions.

### 3.5 Pathology

Careful attention must be paid to the labelling of forms and samples before sending to the Specialist Integrated Haematological Malignancy Diagnostic Service (SIHMDS). Samples are unlikely to be processed unless clearly and correctly labelled.

#### 3.5.1 Bone marrow aspirate and trephine (BMAT)

Slides for morphology to SIHMDS lab as local practice. Congo Red staining of bone marrow trephine samples should be considered in addition to plasma cell immunohistochemistry panel.

## 4 Diagnostic Criteria

### 4.1 Diagnostic criteria for (symptomatic) myeloma

- Monoclonal plasma cells in bone marrow (aspirate or trephine)  $\geq 10\%$
- Serum paraprotein  $\geq 30\text{g/L}$  (if IgM paraprotein exclude lymphoplasmacytic lymphoma)
- Evidence of end organ damage that can be attributed to myeloma. This is termed myeloma-related organ or tissue injury (ROTI) and commonly called the CRAB criteria:
  - **C**: hypercalcaemia (corrected  $\text{Ca}^{2+} > 0.25\text{mmol/L}$  above normal or  $> 2.75\text{mmol/L}$ )
  - **R**: renal impairment (no other cause) creatinine clearance  $< 40\text{ mL per minute}$  or serum creatinine  $> 177\mu\text{mol/L}$
  - **A**: anaemia ( $\text{Hb} < 100\text{g/L}$  or  $< 20\text{g}$  below normal) not due to other causes
  - **B**: bone lesions (lytic lesions or osteoporosis). One or more osteolytic lesion on skeletal radiography, CT, or PET/CT (of at least  $5\text{mm}$ ). If bone marrow has  $< 10\%$  clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement

Additionally, IMWG guidance recommends treatment for patients without CRAB features but one of the following:<sup>9</sup>

- bone marrow plasma cell percentage  $\geq 60\%$
- serum free light chain ratio (involved/uninvolved)  $\geq 100$  (provided absolute involved light chain at least  $100\text{ng/L}$ )
- more than one focal bone lesion on MRI studies (of at least  $5\text{mm}$  diameter).

### 4.2 Diagnostic criteria for smouldering asymptomatic myeloma

- Monoclonal serum protein of  $> 30\text{g/L}$  **and/or**
- $10\text{--}60\%$  or more clonal plasma cells in bone marrow
- Absence of a treatment requiring myeloma defining event.

### 4.3 Diagnostic criteria for monoclonal gammopathy of undetermined significance (MGUS)

- Paraprotein  $< 30\text{g/L}$  and marrow clonal plasma cells  $< 10\%$  and lymphoplasmacytic lymphocytes  $< 10\%$
- No evidence of myeloma-related organ or tissue impairment
- No evidence of other B cell proliferative disorder or amyloid
- Urinary monoclonal protein  $< 500\text{mg/24h}$ .

### 4.4 Diagnostic criteria for solitary plasmacytoma of bone

- A single bone lytic lesion confirmed to be composed of clonal plasma cells on biopsy



- Absence of a clonal plasma cell bone marrow infiltrate using aspirate, trephine and/or flow cytometry (note: clonal plasma cell infiltrate <10% is classified as solitary plasmacytoma with minimal marrow involvement)
- Presence or absence of monoclonal serum or urine protein
- Absence of evidence of plasma cell-related organ or tissue injury.

#### 4.5 Diagnostic criteria for extramedullary plasmacytoma

- Soft tissue mass confirmed to be composed of plasma cells on biopsy
- Absence of a clonal plasma cell bone marrow infiltrate using aspirate, trephine and/or flow cytometry (note: clonal plasma cells infiltrate <10% is classified as solitary extramedullary plasmacytoma with minimal marrow involvement)
- Presence or absence of monoclonal serum or urine protein
- Absence of evidence of plasma cell-related organ or tissue injury.

#### 4.6 Diagnostic criteria for monoclonal deposition disease, including amyloidosis, light chain deposition disease and MGRS

- Biopsy-proven evidence of interstitial protein deposition on tissue biopsy (e.g. amyloid by Congo red stain on rectal biopsy, light chains on renal biopsy by immunohistochemistry or electron microscopy)
- Documentation of underlying monoclonal dyscrasia by abnormal serum/urine free light chains, serum IFE, SPEP and bone marrow as appropriate.

#### 4.7 Diagnostic criteria for POEMS syndrome

This requires the presence of both mandatory criteria with one other major criterion and one other minor criterion.<sup>11</sup>

- Mandatory major criteria:
  - presence of monoclonal plasma cell disorder (e.g. serum paraprotein, usually  $\lambda$  light chain)
  - peripheral neuropathy
- Major criteria (one required):
  - Castleman's disease
  - osteosclerotic bone lesions
  - elevated vascular endothelial growth factor (VEGF)
- Minor criteria (at least one of the following):
  - organomegaly
  - extravascular volume overload
  - endocrine disorder (excluding diabetes mellitus/DM, hypothyroidism)
  - skin changes
  - papilloedema
  - thrombocytosis/polycythaemia.

## 5 Staging and Risk Stratification

Myeloma staging should be according to the International Staging System (ISS) with additional prognostic categorisation gained by the use of cytogenetics/fluorescence in situ hybridisation (FISH). Additionally, patients should be further risk stratified according to age, performance status and other co-morbidities. This will aid the optimal therapeutic choice and also help the team to ensure that the patient is fully informed. Patients with asymptomatic myeloma, monoclonal gammopathy of undetermined significance (MGUS) and solitary plasmacytoma should be assigned to a risk category.

### 5.1 Staging of myeloma

#### 5.1.1 The International Staging System (ISS)

The following criteria are used to define ISS status:<sup>14</sup>

- Stage I – Beta 2 microglobulin <3.5mg/L and albumin ≥35g/L
- Stage II – Neither stage I nor stage III
- Stage III – Beta-2 microglobulin ≥5.5mg/L.

**Table 5.1: The International Staging System**

| Stage | Criteria   | Median survival<br>(based on historic data) |
|-------|--|---|
| I     | Serum $\beta$ 2m <3.5mg/L and serum albumin ≥35g/L | 62 months                                   |
| II    | Neither I nor III                                  | 45 months                                   |
| III   | Serum $\beta$ 2m ≥5.5mg/L                          | 29 months                                   |

Combining the ISS stage with additional data, e.g. FISH appears to further refine prognostic information for individual patient outcomes.<sup>15–17</sup>

#### 5.1.2 Prognostically important genetic lesions in myeloma as detected by FISH/cytogenetics

It is increasingly recognised that the presence of specific translocations, deletions or copy number abnormalities has powerful prognostic value and may aid treatment decisions and patient education. They include abnormalities believed to represent primary aetiological initiating events as well as secondary progression events.

**Table 5.2: Current molecular variables that have important clinical value**

| Lesion   | Prognosis     | Prevalence |
|----------|---------------|------------|
| 17p-     | Poor          | 8%         |
| 1q+      | Poor          | 33%        |
| 1p-      | Poor          | 8%         |
| t(4;14)  | Poor          | 15%        |
| t(11;14) | Neutral       | 19%        |
| t(14;16) | Probably poor | 1%         |

| Lesion        | Prognosis                                    | Prevalence |
|---------------|--|------------|
| t(14;20)      | Poor   | 3.2%       |
| Hyperdiploidy | Neutral                                      | 48%        |
| TP53 mutation | Poor   |            |
| BRAF          | Response to BRAF inhibition / MEK inhibition | 4%         |
| NRAS / KRAS   | Response to MEK inhibition                   | 40%        |

### 5.1.3 Combined ISS/genetic risk groups

Several groups have now defined risk groups based on ISS stage and FISH abnormalities, including UK Myeloma IX data.<sup>17</sup> These risk groups are defined in Table 5.3. Revised ISS criteria are listed beneath this.

**Table 5.3: Defined risk groups**

#### Myeloma IX dataset:

| Risk group               | Group  |
|--------------------------|--|
| <b>Standard risk</b>     | The rest   |
| <b>Intermediate risk</b> | One of: t(4;14), t(14;16), t(14;20), 17p-, 1q+, 1p- and $\beta 2m < 5.5$   |
| <b>High risk</b>         | One of: t(4;14), t(14;16), t(14;20), 17p-, 1q+, 1p- and $\beta 2m \geq 5.5$  |
| <b>Ultra-high risk</b>   | More than one of: t(4;14), t(14;16), t(14;20), 17p-, 1q+, 1p-<br>or<br>GEP of high risk disease<br>or<br>plasma cell leukaemia |

#### Revised ISS (R-ISS):

| Risk group     | Group   |
|----------------|---|
| <b>R-ISS 1</b> | ISS-1 (serum $\beta_2$ -microglobulin level $< 3.5\text{mg/L}$ and serum albumin level $\geq 3.5\text{g/dL}$ ), no high-risk Cytogenetics [del(17p) and/or t(4;14) and/or t(14;16)], and normal LDH level (less than the upper limit of normal range) |
| <b>R-ISS 2</b> | All other combinations (not R-ISS 1 or 3)   |
| <b>R-ISS 3</b> | ISS stage III (serum $\beta_2$ -microglobulin level $> 5.5\text{mg/L}$ ) and high-risk Cytogenetics [del(17p) and/or t(4;14) and/or t(14;16)], or high LDH level  |

### 5.1.4 Monitoring myeloma patients for prognostic variables

- Patients should be reviewed regularly (e.g. every 2–3 months).
- It is suggested that bone marrows aspirate/biopsy should be done at relapse prior to starting a new therapy with repeat FISH (if available).
- Repeat  $\beta_2$ -microglobulin at relapse prior to starting a new therapy.

- Annual whole body diffusion-weighted magnetic resonance imaging (MRI) is recommended for patients with asymptomatic myeloma to monitor for the presence of focal lesions

## 5.2 Asymptomatic/smouldering myeloma

The probability of progression to symptomatic MM requiring treatment is 51% at five years (10% per year for first 5 years), 66% at 10 years (3% per year for the next 5 years) and 73% at 15 years (1% per year from 10 years onward). When the progression-free survival curves of SMM are examined it is clear there are at least two populations of patients, including a group with high risk disease which rapidly progresses to treatment within 2 years, but also a low risk disease group which behaves more like MGUS. There is some evidence that treating high risk SMM early is appropriate. A recent International Myeloma Working Group (IMWG) consensus document has recommended treating asymptomatic myeloma as symptomatic (i.e. initiating SACT) if any of: BM PC% $\geq$ 60%, involved:uninvolved SFL ratio  $\geq$ 100 (with involved light chain level  $\geq$ 100mg/L),  $>1$  focal lesion on MRI studies, are present as these factors are associated with at least 70% risk of progression within 2 years.<sup>9</sup>

### 5.2.1 Risk stratifying asymptomatic myeloma

Several risk models have been developed (Mayo model and Spanish model) which allow identification of patients at high risk for early progression, potentially indicating patients who require more frequent follow-up or earlier treatment intervention. Additionally, the use of a sensitive imaging assessment, such as whole body low dose computed tomography (CT), positron emission tomography-CT (PET-CT), MRI spine/pelvis or diffusion-weighted whole body MRI, allows early identification of focal bone lesions which require earlier intervention.

**Table 5.4: The Mayo SMM risk stratification system<sup>47</sup>**

| Risk Category     | Number of Risk Factors<br>BMPC $>20\%$<br>M-protein $>20$ g/L<br>sFLC ratio $>20$ | Median Time to Progression to Multiple Myeloma |
|-------------------|---|--|
| Low Risk          | 0   | 110 months                                     |
| Intermediate Risk | 1   | 68 months                                      |
| High Risk         | $\geq 2$  | 29 months                                      |

Additionally, several biomarkers have potential early predictive ability for the transformation of smouldering/asymptomatic myeloma to symptomatic disease. This includes increase in serum monoclonal protein by  $\geq 10\%$  on two successive evaluations within a 6 month period (65% probability of progression within 2 years), cytogenetic subtypes t(4;14), 1q amplification or 17p deletion (50% probability of progression within 2 years) and high bone marrow plasma cell proliferative rate.

### 5.3 Monoclonal gammopathy of undetermined significance (MGUS)

Risk stratification of MGUS identifies patients who may require close monitoring for myeloma transformation but may also indicate patients who can have less regular hospital follow-up or be safely monitored by their GP provided clear advice about monitoring and follow-up has been given.<sup>20</sup>

The following factors are markers of early progression and are additive:

- paraprotein  $\geq 15\text{g/L}$
- non-IgG isotype
- abnormal SFLC ratio ( $<0.26$  or  $>1.65\text{mg/L}$ ).

**Table 5.6: Risk stratification MGUS**

| Risk group  | Absolute risk of progression at 20 years, % | Absolute risk of progression at 20 years accounting for death as a competing risk, % |
|---|---|--|
| <b>Low risk</b> (no factors present)                | 5   | 2  |
| <b>Low–intermediate risk</b> (any 1 factor present) | 21  | 10   |
| <b>Intermediate risk</b> (any 2 factors present)    | 37  | 18   |
| <b>High risk</b> (all 3 factors present)            | 58  | 27   |

### 5.4 Solitary bone plasmacytoma and extramedullary plasmacytoma

Criteria to predict for progression of solitary bone plasmacytoma to myeloma based on SFLC and paraprotein level have been devised and it is recommended that this prediction model is used.<sup>21</sup>

A recent study from the Leeds group has also identified evidence of occult marrow disease detected by multiparameter flow cytometry and presence of monoclonal urinary light chains as significant predictors of progression.<sup>22</sup> The IMWG have suggested classifying solitary bone plasmacytoma with evidence of  $<10\%$  marrow clonal plasma cells as solitary bone plasmacytoma with minimal marrow involvement with an estimated 3-year progression rate of  $60\%$ .<sup>9</sup>

Similarly, while the rate of progression from extramedullary plasmacytoma is relatively low, this is significantly increased if there is evidence of clonal marrow plasma cells ( $20\%$  within 3 years) and it is recommended that this is classified as solitary extramedullary plasmacytoma with minimal marrow involvement.<sup>9</sup>

**Table 5.7: Risk stratification**

| Risk group          | Variables   | 5-year progression rate |
|---------------------|---|-------------------------|
| <b>Low</b>          | Normal SFLC ratio<br>Paraprotein $<5\text{g/L}$       | 13%                     |
| <b>Intermediate</b> | Either variable abnormal                              | 26%                     |
| <b>High</b>         | Abnormal SFLC ratio<br>Paraprotein $\geq 5\text{g/L}$ | 62%                     |

## 5.5 Primary AL amyloidosis

A number of risk stratification models for AL amyloid have been developed and these are mainly based on biomarkers of cardiac involvement and the serum free light chain.<sup>5</sup> The Mayo Clinic has recently updated its prognostic scoring model which utilises Troponin T, NT-pro BNP to identify three prognostic groups.<sup>23</sup>

A score of 1 is assigned for each prognostic variable: Cardiac Troponin T  $\geq 0.03\text{ng/ml}$ , NT pro-BNP  $>335\text{pg/ml}$ . Note, the Estimated Median OS is based on the Mayo Clinic's initial modelling and requires formal validation to ensure accuracy.

**Table 5.8: Risk stratification for AL amyloid**

| Stage   | Estimated Median OS | 95% CI   |
|---|---------------------|----------|
| <b>Stage I</b>  | 94 months           | 64 – 154 |
| <b>II</b>   | 40 months           | 24 – 59  |
| <b>IIIa (NT-proBNP <math>&lt;8500\text{pg/mL}</math>)</b> | 14 months           | 11 – 18  |
| <b>IIIb (NT-proBNP <math>&gt;8500\text{pg/mL}</math>)</b> | 5.8 months          | 5 – 7    |

## 6 Treatment of Myeloma and Related Disorders

### 6.1 Principles of myeloma treatment

The aim is to maximise response rates and by so doing maximise progression-free survival and overall survival. The phases of treatment that can be used to achieve this include:

- induction
- stem cell harvesting
- high dose melphalan and autologous stem cell transplantation (ASCT)
- post-transplant consolidation
- ongoing treatment.

The choice of treatment depends upon:

- the performance status of the patient
- their frailty index and the presence of co-morbidities
- prior exposure to systemic anti-cancer treatment (SACT)
- high risk disease determined by FISH status.

Treatment should be started as soon as possible once the diagnosis is made and the aim is to intervene therapeutically early in the disease course to prevent end organ damage.

### 6.2 Myeloma supportive care

Optimal supportive treatment is an essential component of the overall clinical management. Brief guidance for supportive treatment is given in this document; however, reference should be made to the BSH *Guidelines for supportive care in multiple myeloma* (2011).

- Advice regarding maintaining good hydration should be given.
- Effective pain control management is imperative. The symptom control/palliative care team can be contacted for advice if required. NSAIDs should be avoided.
- Patients should have a dental assessment before starting treatment with bisphosphonates if possible. The risk of osteonecrosis of the jaw should be discussed prior to commencing bisphosphonates.
- For all treatment regimens, dose reduction should be avoided and dose intensity maintained using GCSF. However, there needs to be care that future stem cell reserve is not compromised.
- In order to prevent tumour lysis and protect renal function, allopurinol will be used at the beginning of every first cycle regardless of the SACT regimen.
- Infection prophylaxis:
  - Aciclovir should be given to all patients receiving bortezomib, DT-PACE or an ASCT and should be continued for at least 3 months post therapy.
  - Azole prophylaxis may be considered in regimens containing high-dose steroids

- Levofloxacin should be considered for at least the first 3 months of induction therapy and co-trimoxazole could be added in this situation depending on local sensitivities
  - Co-trimoxazole is required for all ASCT patients, those receiving high dose dexamethasone and all patients recovering from intensive SACT, e.g. VTD-PACE (as per local practice).
- Serological testing for Hepatitis B is recommended for patients starting treatment with lenalidomide, carfilzomib, pomalidomide, bortezomib and daratumumab and should be considered before commencing any new line of therapy. If previous exposure is demonstrated, prophylaxis with tenofovir or lamivudine depending on local hepatology advice is recommended for the duration of treatment, with regular PCR monitoring of HepB viral copy number. Discussion with a Hepatologist may also be considered in this situation, and is mandated if raised viral copy numbers are detected.
- Patients should receive regular bisphosphonate therapy (see below).

### 6.3 Patient information support and role of CNS/key worker at diagnosis

- The clinical nurse specialist (CNS) will be involved with the management of all myeloma patients. Their role is to offer emotional support, information and practical advice from the time of diagnosis throughout the course of treatment and aftercare. In most cases the CNS will be the patient's key worker.
- The CNS should be present at diagnosis and at any significant discussion of treatment changes and outcomes. All patients should have a card documenting the CNS/key worker's name and contact details, together with an out-of-hours contact for urgent advice.
- Patients should be informed appropriately about their condition, its potential complications and the importance of supportive measures. They should also have information about treatment options. They should be offered written information booklets, and be informed of local and national support services, such as Myeloma UK and Macmillan Cancer Support.
- The CNS/key worker should also provide support to family members and significant others at diagnosis, ensuring the principles of patient confidentiality are maintained.
- The CNS/key worker should be available to the patient either in person, by telephone or by email to address any questions or concerns and to provide ongoing support.
- The CNS should ensure that all patients are offered a Holistic Needs Assessment (HNA) within 31 days of diagnosis. Following the HNA, every patient should be offered a written care plan associated with the HNA which should be developed with the patient and communicated to appropriate healthcare professionals.
- More detailed information about the role of the CNS/key worker can be found in [section 8: Supportive Care and Common Treatment-related Complications](#).



## 6.4 Assessment of response

### 6.4.1 Timing of response assessments

#### *During treatment*

- Serum or urine paraprotein quantitation, as appropriate, at the start of each treatment cycle and before high-dose therapy.
- Serum free light chain (SFLC) test can be used for assessment:
  - at baseline in all patients, at the start of each cycle and for monitoring for relapse, but it is especially useful to assess response in amyloidosis
  - light chain myeloma
  - oligosecretory disease (when paraprotein <10g/L on serum protein electrophoresis/SPEP).
- Bone marrow biopsy: post-induction treatment, prior to stem cell transplantation.

#### *Following high dose therapy and when off treatment*

- Serum and urine paraproteins (as appropriate) or SFLC at 2 to 3 monthly intervals
- Full blood count (FBC) and urea and electrolytes (U&E)
- Bone marrow assessment at 3 months and then at possible relapse as discussed in [section 3.1.4](#)
- Repeated imaging (e.g. positron emission tomography-computed tomography/PET-CT, magnetic resonance imaging/MRI or whole body diffusion-weighted MRI) may also be appropriate.

*The time at which response is assessed must be documented. Appropriate time points include:*

- post-induction
- pre-harvest/pre-transplant
- post-ASCT (day 100)
- 1-year post-ASCT
- at the end of a treatment line/course
- at relapse.

### 6.4.2 The International Myeloma Working Group (IMWG) response criteria

The IMWG response criteria<sup>24</sup> should be used (see [Table 6.1](#)) and the response monitored using:

- serum and urine electrophoresis with immunofixation to confirm complete response
- SFLC analysis (where appropriate and if complete remission/CR is suspected)
- bone marrow aspirate and trephine with immunohistochemistry or flow cytometry to confirm clonality

- All patients in clinical CR must have a bone marrow assessment to confirm complete response.
- Flow cytometry for minimal residual disease if a patient is in CR is important in order to define an MRD negative response which is an important end point and indicator of outcome. Molecular tests could be performed as an alternative, if available. For both methods the minimum level of sensitivity should be  $1 \times 10^{-5}$ .
- PET-CT or diffusion weighted MRI should be considered to confirm resolution of focal bone lesions or extramedullary disease.
- Relapse is indicated by the patient achieving the definitions provided above.
- Clinical progression occurs when related organ or tissue injury (ROTI) develops.
- Treatment will be initiated to prevent the development of ROTI at the time of biochemical progression if indicated clinically.

**Table 6.1: IMWG definitions of response**

|   |   |
|---|---|
| <b>MRD Negative</b>                       | Subgrouped as:<br>1. Flow MRD- : No clonal cells in bone marrow aspirate by flow $1 \times 10^5$ sensitivity<br>2. Molecular MRD- : No clonal cells in bone marrow aspirate by NGS at $1 \times 10^5$ sensitivity<br>3. Imaging and MRD- : Disappearance of previously defined increased tracer uptake to <mediastinal pool SUV or background tissue plus MRD- by flow or NGS<br>4. Sustained MRD- : MRD- by flow and/or NGS and negative PET/CT confirmed at 1 year timepoints |
| <b>Complete remission (CR)</b>            | Negative immunofixation on serum and urine<br>Disappearance of any soft tissue plasmacytomas<br><5% plasma cells in bone marrow   |
| <b>Stringent complete remission (sCR)</b> | As above and:<br>Normal SFLC ratio and no evidence of clonal plasma cells on immunohistochemistry   |
| <b>Very good partial response (VGPR)</b>  | >90% reduction in serum paraprotein and <100mg/24h BJP  |
| <b>Partial response (PR)</b>              | >50% reduction in serum paraprotein and/or >90% reduction in BJP and/or $\geq 50\%$ decrease in difference between involved and uninvolved SFLC and/or >50% decrease in bone marrow plasma cells (if non-secretory multiple myeloma)  |
| <b>Stable disease/no response (SD)</b>    | None of the above and not progressive disease<br>Define the time to progression   |
| <b>Progressive disease (PD)</b>           | >25% increase in serum paraprotein (absolute increase >5g/L)<br>Urinary BJP (absolute increase >200mg/24h)<br>Difference between SFLC (absolute increase >100mg/L)<br>Bone marrow plasma cells (absolute >10%)<br>New bone lesions/plasmacytomas<br>Myeloma-related hypercalcaemia  |
| <b>Primary refractory</b>                 | Defined as having never achieved partial response on therapy (PR)<br>Non-responding, non-progressive<br>Progressive disease   |
| <b>Relapsed/refractory</b>                | Achieved partial response on therapy (PR) then progressed within 60 days  |
| <b>Relapsed</b>                           | Developed progressive disease after initially achieving partial response with >60 days duration and occurs off therapy  |

## 6.5 Systemic anti-cancer treatment (SACT) for myeloma

The selection of treatment for myeloma is dependent upon several features including age, disease subtype and performance status.

The important clinical subtypes of myeloma are laid out below:

- transplant eligible

- plasma cell leukaemia
- transplant non-eligible
- severe renal failure
- solitary plasmacytoma
- multiple solitary plasmacytoma
- extramedullary plasmacytoma.

For patients, the aim is to maximise depth of response and improve progression-free survival and overall survival.

Autologous stem cell transplantation is the standard of care for suitable patients based on response and medical fitness.

For frail patients, disease control using a safe tolerable regimen that has a low mortality rate is an important consideration.

Individual treatment regimens are given in [Annex 1](#).

All patients should be considered for entry into a clinical trial at each of their disease stages. If a trial is not available locally consider referral to a unit where the trial is open to recruitment.

### **6.5.1 First-line systemic anti-cancer treatment**

The choice of first-line therapy for myeloma depends on the patient's suitability to undergo subsequent stem cell transplantation. Therefore, patients are considered to be transplant eligible (TE) or transplant ineligible (TNE).

All patients should be assessed for transplant suitability on the basis of performance status, co-morbidities and age. TE patients should be treated with an intensive approach. The use of high dose melphalan with subsequent autologous stem cell support is the treatment of choice. TNE patients should be treated with a non-intensive approach. Frail patients where treatment can have significant morbidity and mortality should receive dose reduced TNE treatment.

#### **6.5.1.1. Transplant eligible patients**

Myeloma therapy for younger, fitter patients follows several distinct phases including:

- induction
- stem cell mobilisation and harvesting
- autologous stem cell transplantation (ASCT)
- post-transplant consolidation
- maintenance/ongoing treatment.

In this setting, SACT induction is given to achieve rapid cytoreduction.

An induction regimen that has anti-myeloma activity but is not stem cell toxic should be used.

Achievement of CR before or after autologous transplant is associated with superior progression-free and overall survival.

The initial aim of therapy is therefore to administer adequate induction therapy to maximise the depth of response.

a) *Induction*

- Entry into a clinical trial is the preferred option, if available. If unavailable locally, consider referral to a unit that has a clinical trial open.
- For non-clinic trial entry, bortezomib based-therapy ((VTD recommended, but can consider CVD).<sup>25, 26</sup> CTD can be considered if bortezomib administration is not appropriate or acceptable to the patient.<sup>27</sup>
- Doublets are generally less effective than triplets.
- Achievement of at least a VGPR is optimal before proceeding to stem cell harvesting, however the need to deepen response in a patient with PR should be balanced against the cumulative toxicity of further therapy, the effect on stem cell reserve, and patient fitness/co-morbidities.
- Bortezomib-based triplets and combinations such as VTD and infusional regimens such as VDT-PACE should be considered for patients with ultra-high risk disease<sup>17</sup>. Consolidation following induction therapy can also be considered.

b) *Stem cell mobilisation and harvesting*

- Early referral to the transplant team is advised to allow for scheduling of stem cell mobilisation immediately following attainment of maximum response.
- Several mobilisation regimens can be used. However, a chemotherapy-based priming approach is generally preferred with cyclophosphamide/GCSF, although alternative priming strategies can be used (e.g. etoposide, cytarabine or GCSF alone).
- Patients who have failed prior mobilisation attempts or are predicted to be poor mobilisers (e.g. previous autograft) are eligible to undergo mobilisation with the CXCR4 antagonist plerixafor.
- A minimum of  $2 \times 10^6$  CD34+ cells/kg is required to undergo autologous transplant based on local practice. Alternatively, a minimum of  $20 \times 10^4$  CFU-GM/kg, when colonies are assessed (based on local practice).
- Younger patients may undergo a second autograft at relapse, hence consider a minimum target of at least  $4 \times 10^6$  CD34+ cells/kg. Ideally these should be collected at the end of induction and stored rather than collecting cells at first or second relapse.

c) *Autologous stem cell transplant**ASCT for TE patients*

- All medically fit patients should be considered for high-dose melphalan ( $200\text{mg/m}^2$ ) and autologous stem cell rescue as part of their first-line therapy.
- ASCT should proceed in patients who attained at least a PR following induction therapy.
- ASCT is associated with complete remission rates varying between 25% and 60%, a low treatment-related mortality (TRM) (<2%) and a median survival of approximately 5–10 years.
- Patients who relapse >18 months following a first autograft and continue to be medically fit can be considered for second autologous transplant.

- Advice concerning physical activity and nutritional status should be given and referral to the appropriate members of the multidisciplinary team (MDT) as required.
- Specific pre-transplant medical assessment should be carried out.

Conditioning regimens:

- Melphalan 200mg/m<sup>2</sup> is recommended although a dose reduction based on glomerular filtration rate (GFR) or age/co-morbidities may be required.
- Consider melphalan 140mg/m<sup>2</sup> for those patients who are older or those with associated co-morbidities.
- Split dose melphalan may be used as appropriate.

### *ASCT for amyloid and POEMS*

A risk-stratified approach in AL amyloid is taken in terms of patient selection for ASCT and dose selection. Refer to the BSH guidelines on amyloidosis. Amyloidosis transplants should be undertaken in centres performing at least five such transplants each year.

### *Tandem ASCT*

Some clinical trial evidence has suggested that tandem autografts may increase depth of remission after first high dose chemotherapy, particularly in those who have not achieved a complete remission, and this may lead to improved progression-free survival.<sup>28, 29</sup> Tandem ASCT can be used in appropriate settings as per BSBMT guidance and there may be specific benefit in patients with cytogenetically defined high risk disease

### *ASCT in severe renal failure*

Autologous transplant may be considered for patients with severe renal impairment (creatinine clearance <30ml/min).

- The TRM for patients with a creatinine clearance of 10–30ml/min and who are dialysis-independent is low with careful patient selection.
- The TRM for patients on dialysis is higher, so although it can be performed in this situation it requires very careful patient selection and discussion.
- Dose reduction based on creatinine clearance should be considered, as per local guidelines.
- Early involvement of the renal team is important.

### *d) Allogeneic stem cell transplant*

Although it is recognised that the majority of patients with myeloma are not suitable for an allogeneic approach, there are a number of settings and approaches for allogeneic transplantation. It is preferred that this occurs within the context of a suitable clinical trial. Allograft can be considered at the following times:

- at presentation in younger patients
- at first and subsequent relapse.

Both myeloablative and non-myeloablative reduced intensity conditioned transplants can be considered according to individual transplant centre policy and in line with local transplant guidelines.

### e) *Post-transplant consolidation*

A number of clinical trials demonstrate that:<sup>30</sup>

- blocks of treatment post-ASCT can improve response rates – evidence for this predominantly comes from investigating the role of VTD, which is associated with increasing CR rates and improving progression-free survival<sup>31</sup>
- alkylating agents should be avoided post-ASCT
- bortezomib, if used for induction, may also be of benefit when used post-transplant when given in combination with other agents.

Currently, neither post-transplant consolidation nor maintenance post-transplant is NHS funded.

### f) *Post-transplant maintenance*

- Thalidomide can be effective in the maintenance treatment setting if the patient is known to have standard risk disease defined by molecular techniques. However, it is difficult to tolerate and most patients can only tolerate 50mg for <12 months.<sup>30, 32</sup>
- Interferon has been shown to be effective in the setting but is associated with impaired quality of life.
- Lenalidomide has been shown to be effective as a maintenance regimen. It is licensed but unfunded in the NHS. Meta-analysis of three large studies shows an improvement in both PFS and OS (Attal *et al.*, ASCO, 2016)
- Bortezomib has been shown to be effective as a maintenance regimen. It is unlicensed and unfunded for this indication in the NHS.
- Ixazomib has been shown to be effective as a maintenance regimen. It is unlicensed and unfunded for this indication in the NHS.

Currently neither post-transplant consolidation nor maintenance post-transplant is NHS funded.

### g) *Ultra-high risk disease in TE patients*

Ultra-high risk patients (as defined by Boyd *et al.*, *Leukaemia*, 2012) have a particularly poor outcome and can be treated intensively where clinically appropriate with the aim of achieving MRD negative status and attempting to maintain remission:

- intensive bortezomib-based induction regimens such as VTD-PACE or VTD induction
- melphalan autologous transplant; consider the use of tandem autograft
- consolidation with VTD or bortezomib should be considered
- entry into clinical trials
- consider novel agents, as well as allogeneic transplantation in suitable patients.

### h) *Plasma cell leukaemia*

Plasma cell leukaemia may be primary (60%) or secondary (40%) and is defined as the presence of >20% circulating plasma cells or an absolute level of  $2 \times 10^9/L$  plasma cell in the peripheral blood.

Plasma cell leukaemia should be considered as an ultra-high risk disease setting. All patients with plasma cell leukaemia should be managed in centres with appropriate expertise and relevant clinical trials.

Several intensive combination approaches have been described for plasma cell leukaemia including VTD-PACE and VTD<sup>35</sup>.

Where appropriate, early consolidation using autologous transplant should be carried out.

Allogeneic transplant may be appropriate in this setting but should not be done unless a stable remission can be induced.

Entry into clinical trials where available.

#### *6.5.1.2. Transplant non-eligible patients*

- The goal of non-intensive treatment for myeloma is the sustained control of disease with long progression-free survival and overall survival while maintaining quality of life.
- Wherever possible, patients should be offered entry into a clinical trial.
- Treatment should be chosen according to co-morbidities and performance status.
- Fluorescence in situ hybridisation (FISH) retains prognostic value in this patient group.

#### *a) Induction*

Lenalidomide given as first-line therapy in TNE patients shows an improved PFS when given continuously, compared to MPT or lenalidomide stopped after 18 months. Furthermore, continuous lenalidomide is associated with an improved OS, compared to MPT<sup>39</sup>. It is NICE approved and recommended as first line therapy.

Based on clinical trial evidence, treatment with bortezomib/alkylator/corticosteroid (e.g. VMP) is also recommended as first-line therapy, and patients should receive up to 9 cycles.<sup>36, 37</sup> An alternative is CVD.

When deciding between Lenalidomide/dexamethasone vs bortezomib/alkylator/corticosteroid consider patient factors (oral vs SC administration) and risk factors (high risk disease may benefit from triplet/bortezomib treatment).

.

Performance status and frailty indices are important prognostic factors and may be more important than molecular tests in the elderly age group.

#### *b) Ongoing treatment post-induction*

Maintenance therapy following induction has been associated with improving progression-free survival and possibly overall survival in this patient group. In addition potential benefits in terms of PFS must be weighed carefully against the risk of adverse events and ongoing therapy.<sup>30</sup>

Thalidomide in non-high risk patients can be considered, although even at low dose (50mg/day) it is poorly tolerated for prolonged therapy.

Lenalidomide maintenance has been demonstrated to be associated with significant improvement in progression-free survival following IMiD-based induction in this setting and can be considered.<sup>40</sup> However, it should be noted that there is no improvement in overall survival, it is currently neither



licensed nor NICE approved for this indication and was associated with relatively high rates of second malignancy.

### 6.5.1.3. *Patients with severe renal failure*

Up to 30% of newly diagnosed patients present with evidence of renal impairment (creatinine  $>200\mu\text{mol/L}$ ) and renal failure is associated with a reduction in response rate, progression-free survival and overall survival rates.

- Early involvement of a consultant nephrologist is recommended for advice on renal support and possible renal replacement therapy. Consider a renal biopsy if the course is unclear or there is more than 0.5g/24 of albuminuria.
- Reversal of renal failure is of paramount importance and may be achieved by rapid reduction of light chain load.
- The use of apheresis/dialysis has not consistently been shown to be of benefit and should only be carried out in the context of a clinical study or for symptomatic control.

Following confirmation of a diagnosis of myeloma, therapy should be initiated immediately.<sup>41</sup>

- Bortezomib, thalidomide, cyclophosphamide, doxorubicin and dexamethasone (e.g. PAD, CVD, VTD) combinations are appropriate in this setting and require no or minimal dose modification in renal failure.
- Emerging evidence suggests that bortezomib-containing regimens are particularly effective at inducing an early reduction of light chains with potential for reversal of renal failure.<sup>26</sup>
- For patients for whom salvage of renal function remains a possibility, regular SFLC should be monitored (consider weekly, pre-dialysis) and in the absence of improvement in renal function or significant reduction in light chain load, consideration should be given to using salvage therapy with a second-line therapy.
- Standard frontline therapeutic regimens can be utilised but often require dose modifications as a result of the reduced glomerular filtration rate.
- Melphalan should be dose reduced by 50% if GFR  $<40\text{ml/min}$  with increases in melphalan dose in subsequent courses as tolerated.
- Cyclophosphamide should be administered at 75% dose if GFR 10–50 ml/min and 50% dose if GFR  $<10\text{ml/min}$ .
- Lenalidomide requires dose adjustment depending on the degree of renal impairment according to manufacturer's algorithm.
- High dose SACT and stem cell transplant can be carried out in patients receiving regular dialysis; improvement/reversal of renal dysfunction may occur. However, morbidity and mortality are high. Close liaison between the renal and transplant teams is essential.

## 6.5.2 Primary refractory disease

Patients who have never achieved an MR to initial therapy and progress while on therapy are defined as primary refractory.

Treatment for this group of patients is difficult, particularly if they have already received and are resistant to the above-mentioned therapies. Patients should be considered for early phase clinical

trials. Novel combinations of previously received therapies may be appropriate, or single agent alkylating or corticosteroids with palliative intent.

#### 6.5.2.1. *Primary refractory – intensive approach*

Primary refractory disease is rare with current therapeutic approaches.

- Treatment with bortezomib-based therapies are appropriate if a thalidomide first-line therapy has failed and should be given to maximise response prior to stem cell harvesting and ASCT.
- If primary refractory to a bortezomib-based induction, consider dose intensification (VTD-PACE) or use of a lenalidomide-based combination therapy (e.g. CRD).
- Triplets are more effective than doublets and combination regimens (e.g. VTD, VTD-PACE) can be appropriate in certain settings.
- The aim should be to get patients to ASCT with high dose melphalan, with consolidation after this.
- Entry into clinical trials with novel agents is important for this group of patients

#### 6.5.2.2 *Primary refractory disease – non-intensive approach*

Primary refractory disease is more common in this group of patients.

- Treatment with bortezomib-based therapies is appropriate if a thalidomide first-line therapy has failed.
- If primary refractory to a bortezomib-based induction, consider dose intensification or use of a lenalidomide-based combination therapy (e.g. CRD).
- Triplets are more effective than doublets but in this setting toxicity needs to be considered.
- Care should be taken in frail patients or patients with a low performance status or co-morbidities.
- Entry into clinical trials is important for this group of patients.

#### 6.5.2.3. *Relapsed disease*

- With each successive relapse the progression-free survival becomes shorter.
- Relapse may occur with a rise in light chains only in patients who previously had a detectable paraprotein, a phenomenon known as light chain escape.
- At each relapse the disease becomes more resistant.
- At each relapse patients should be considered for clinical trial entry.
- Aim to swap to a therapy with different mechanisms of action if possible.
- If a long PFS is seen with a treatment it may be appropriate to use it again at relapse.
- Relapse on ongoing treatment is a special situation and needs to be managed appropriately.
- Patients should be enrolled in clinical trials where appropriate.

#### *First relapse*

- The aim is to maximise response and prolong progression-free survival.

- Daratumumab/bortezomib/dexamethasone is available via the Cancer Drug Fund in this setting and is recommended at first relapse. Consider giving bortezomib on a weekly basis within this regimen to reduce the risk of neurotoxicity.
- Lenalidomide/dexamethasone is an option if patients did not receive lenalidomide at induction
- Carfilzomib is recommended by NICE for patients who have not received a prior bortezomib-based regimen.
- Triplet combinations are more effective than doublets.
- Autologous transplant as consolidation can be considered provided the patient is medically fit and first transplant progression-free survival was longer than 12 months, or ASCT was not used at first response (NB NHS commissioning supports 2<sup>nd</sup> transplant if PFS at least 18 months)
- 

### *Second relapse*

- Lenalidomide is indicated by NICE at second and subsequent relapse:
  - Triplet therapy is more effective than doublet therapy.
  - Ixazomib given in combination with lenalidomide and dexamethasone improves progression-free survival in a recently published phase 3 study. It is available via the Cancer Drugs Fund, with lenalidomide available via routine commissioning. It is well tolerated and should be considered the standard of care for patients with relapsed myeloma (available for patients at 2<sup>nd</sup> or 3<sup>rd</sup> relapse), even those who are elderly or frail. Nausea, other GI side effects, and thrombocytopaenia are usually mild and manageable toxicities.
  - Addition of cyclophosphamide to lenalidomide and dexamethasone could also be considered.
  - Addition of daratumumab, elotuzumab or carfilzomib to RD improves progression-free survival in recently published phase 3 studies. These are licensed, but unfunded by NHS England.
  - Treatment should be continued to maximal response and then the dexamethasone stopped and lenalidomide continued as a single agent until disease progression.
  - At biochemical progression, dexamethasone or cyclophosphamide can be added back into the backbone of lenalidomide therapy.
- Bortezomib dexamethasone panobinostat:
  - NICE approved for patients who have received at least two lines of therapy including bortezomib and an immunomodulatory agent (see below).

### *Third and subsequent relapse*

- Daratumumab and dexamethasone
  - Daratumumab monotherapy is available via the Cancer Drugs Fund at 3<sup>rd</sup> relapse (fourth-line) only. Phase 2 data supports its use as monotherapy with patients with relapsed myeloma who are refractory to conventional therapies. It is important to consider this treatment at 3<sup>rd</sup> relapse as this therapy will be unavailable at any other relapse.

- Daratumumab is a monoclonal antibody given as slow IV infusion (around 7 hours). In the absence of infusion reactions (breathing problems and hypotension, which are unusual), the infusion time can be accelerated subsequently (3 to 4 hours). It is given weekly for 8 weeks, then fortnightly for 16 weeks and monthly after this. It is given in combination with dexamethasone.
- Fast (90 minute) infusions are safe from the third infusion onwards if the patient has not reacted to the previous infusion. Subcutaneous daratumumab is effective and safer than IV and
  - Daratumumab binds to CD38 on red cells that means additional testing is required for cross matching. Prior to starting daratumumab, clinicians should request a group and save, antibody screen and extended red cell phenotype (or according to local guidelines).
  - The addition of daratumumab to lenalidomide, pomalidomide, bortezomib or carfilzomib improves the efficacy of these agents based on recently published trials. Daratumumab with lenalidomide or bortezomib is licensed. Only the combination with bortezomib is funded on the NHS, specifically as 2<sup>nd</sup> line therapy.
- Bortezomib dexamethasone panobinostat
  - NICE approved for patients who have received at least two lines of therapy including bortezomib and an immunomodulatory agent.
  - Consider for patients who have responded to bortezomib before, without significant toxicities, and have achieved a durable response (at least 6 months).
  - Bortezomib should be given on a weekly basis, to reduce issues with neuropathy.
  - Consider giving panobinostat on alternative weeks (days 1, 3, 5 and 15, 17, 19 of a 28-day cycle), and counsel patients about the possible GI side effects. Dose adjust according to the common toxicities, namely GI and thrombocytopaenia, as per the SPC.
  - Addition of thalidomide to VD panobinostat may improve efficacy.
  - Patients can receive up to 16 cycles (48 doses), noting the frequency of bortezomib changes to fortnightly from cycle 9 onwards.
- Lenalidomide and dexamethasone
  - If not used before, should be considered, with the addition of ixazomib as mentioned before.
- Pomalidomide combinations
  - NICE approved for patients who have received at least 3 lines of therapy, including both lenalidomide and bortezomib.
  - No dose modification is needed for those patients with renal impairment (unlike lenalidomide).
  - Triplets such as cyclophosphamide PD or clarithromycin PD, are more effective than PD. Aim to start triplet therapy at initiation of treatment.
  - Treatment should be continued and avoid withdrawing dexamethasone unless unacceptable toxicities.
- Bendamustine combinations
  - Available on the Cancer Drugs Fund.

- Addition of thalidomide to bendamustine dexamethasone may have superior efficacy.
- No dose modification is needed for those patients with renal impairment.
- Use other novel combinations including VTD and VRD.
- Use conventional chemotherapy combinations such as intermediate dose melphalan.
- Patients should be entered into clinical trials.

### 6.5.3 Solitary plasmacytoma

- The treatment of choice is localised radical radiotherapy but detailed imaging (WB-MRI or PET-CT) is mandatory.
- Rapid referral/close liaison with the clinical oncology team is recommended.
- In some instances (e.g. large plasmacytoma or patients with high risk disease) it may be appropriate to consider myeloma-like treatment or high dose therapy.
- Following treatment, patients will be reviewed in the MDT meeting to allow the response assessment to be formally recorded.
- Consider clinical trials for these patients (IDRIS trial).
- Following treatment, regular whole body imaging with wbMRI or PET/CT is recommended at a minimum of one a year for 5 years. Consider performing more frequently in the first two years after treatment when the risk of relapse is highest.

**Table 6.2: Myeloma treatment options**

|                      |   |
|----------------------|---|
| <b>First line</b>    | <ul style="list-style-type: none"> <li>• Bortezomib based prior to ASCT TA311 – transplant appropriate</li> <li>• Lenalidomide TA587 for non-transplant eligible</li> <li>• Bortezomib or thalidomide TA228 – non-transplant appropriate</li> </ul>   |
| <b>Second line</b>   | <ul style="list-style-type: none"> <li>• Daratumumab/bortezomib (CDF)</li> <li>• Bortezomib TA129 (lenalidomide removed from CDF)</li> <li>• Carfilzomib TA10005 (no prior bortezomib)</li> <li>• Lenalidomide TA586 (prior bortezomib)</li> <li>• Consider second ASCT (if appropriate)</li> </ul> |
| <b>Third line</b>    | <ul style="list-style-type: none"> <li>• Lenalidomide TA171 with ixazomib (CDF)</li> <li>• Bortezomib with panobinostat TA380</li> </ul>  |
| <b>Fourth line +</b> | <p>Options:</p> <ul style="list-style-type: none"> <li>• Daratumumab – fourth line only (CDF)</li> <li>• Bortezomib with panobinostat TA380</li> <li>• Lenalidomide TA171 with ixazomib (CDF)</li> <li>• Pomalidomide TA427</li> <li>• Bendamustine</li> <li>• Clinical trials</li> </ul>           |

### 6.5.4 Multiple solitary plasmacytoma of bone

- In many instances it is appropriate to treat patients with multiple plasmacytoma as myeloma.

- This rare situation requires specific MDT discussion.

### **6.5.5 Extramedullary plasmacytoma**

It is important to check histology on these cases. Cases located in the head and neck, solitary in nature with no history of previous myeloma, are often related to marginal zone lymphomas.

Treatment can involve local radiotherapy or treatment as per approaches used in marginal zone lymphomas.

## 7 Management of Myeloma Emergencies and Complications

### 7.1 Spinal cord compression pathway

Based on local guidelines.

- Spinal cord compression due to malignant infiltration or vertebral collapse requires immediate management and referral.
- Spinal cord compression is best investigated by magnetic resonance imaging (MRI) to define the site and extent of tumour. An assessment of spinal stability can also be made. If MRI is not possible then urgent computed tomography (CT) scan should be performed.
- If there is evidence of spinal cord compression, the patient should be discussed and follow the treatment pathway for cord compression in myeloma.
- Dexamethasone 40mg daily or methyprednisolone 1.5g should be commenced immediately.
- Refer as a matter of urgency to the on-call clinical oncologist (<24 hours) for consideration of local radiotherapy.
- Where appropriate, discussion should also be undertaken with the on-call neurosurgical team for consideration of the appropriateness of surgical decompression or the orthopaedic team for discussion about spinal stability.
- Referral to the multidisciplinary team and allied healthcare professionals should be considered for support and rehabilitation from neurological deficits.

### 7.2 Hypercalcaemia

- Mild hypercalcaemia can be corrected with fluid replacement using intravenous normal saline.
- Severe hypercalcaemia ( $\geq 2.9$  mmol/L) should be corrected using intravenous fluid and an intravenous bisphosphonate (e.g. zoledronic acid 4mg). For those with renal impairment a modified dose of pamidronate or denosumab can be considered.
- Bisphosphonate therapy may need to be repeated after 3–5 days if hypercalcaemia is not controlled. Zoledronic acid is the most effective but may require dose adjustment if there is renal impairment for subsequent doses.
- Bisphosphonate contraindicated or refractory patients may respond to corticosteroids.
- Systemic anti-cancer treatment (SACT) should be initiated rapidly.
- For bisphosphonate and corticosteroid refractory patients, consideration can be given to the use of calcitonin or denosumab.

### 7.3 Hyperviscosity

- Hyperviscosity may develop in patients with high serum paraproteins and can be associated with blurred vision, headaches, mucosal bleeding and dyspnoea due to heart failure.
- Measure plasma viscosity (PV) level. A level <5 mPa is not normally associated with hyperviscosity.
- Intravenous fluids and SACT should be instituted promptly.

- Consider urgent 1–1.5 volume plasmapheresis using saline and albumin replacement.
- If plasmapheresis is not immediately available but there is significant hyperviscosity, consider isovolaemic venesection with N. saline IV fluid replacement.
- Measure PV pre- and post-intervention.
- Avoid red cell transfusion if possible. If red cell transfusion is necessary, exchange transfusion should be performed.

## 7.4 Renal failure

This is often multifactorial but is often related to the light chain load and can be potentiated by hypercalcaemia, dehydration, infection and the use of nephrotoxic drugs.

- Adequate hydration should be maintained in all patients (fluid intake >3L/day), to preserve renal function.
- Potentially nephrotoxic drugs (e.g. non-steroidals, radiographic contrast agents, aminoglycosides) should be avoided.
- Close liaison with the renal team is recommended for patients with impaired renal function/established renal failure.
- Consider rapid SACT if renal failure is directly due to cast nephropathy or light chain/amyloid deposition. Initial therapy with dexamethasone 40mg OD for 4 days or methylprednisolone 1.5g IV daily followed by prompt combination SACT.

## 7.5 Infection

- Myeloma is associated with an increased risk of infection as a result of deficits in the immune system and as a complication of treatment.
- Levofloxacin has been shown to reduced infection rates during the first 3 months of induction therapy and is recommended. Co-trimoxazole in combination with levofloxacin may have conferred additional benefit and should be considered.
- Febrile events should be treated promptly with broad spectrum antibiotics. Intravenous antibiotics are required for severe infection and neutropenic sepsis.
- Aminoglycosides should be avoided if possible to reduce the risk of renal impairment.



## 8 Supportive Care and Common Treatment-related Complications

Common treatment-related complications include:

- Anaemia
- Bleeding – severe thrombocytopenia
- Bleeding – coagulopathy
- Peripheral neuropathy
- Radiotherapy
- Pain management
- Bone disease
- Thromboprophylaxis for patients on IMiD drugs (thalidomide, lenalidomide and pomalidomide)
- Infections and antimicrobial prophylaxis
- Diarrhoea on long-term IMiDs
- Disease-specific complications to WM.

### 8.1 Anaemia

Anaemia is a common problem either at diagnosis or later in the disease course. It is often multifactorial due to marrow infiltration, renal impairment, vitamin deficiency and systemic anti-cancer treatment (SACT) induced marrow suppression. Anaemia often improves following disease control by SACT.

- Patients with symptomatic anaemia can be treated with regular blood transfusions in the short term.
- Anaemia associated with renal impairment may respond to erythropoietin and should be managed in conjunction with a renal physician.
- For patients with persistent symptomatic anaemia (haemoglobin/Hb <10g/dl) and in whom haematinic deficiency has been excluded, a trial of erythropoietin should be considered. The dose can be doubled after 4 weeks if Hb increased <1g/dl. The target Hb should be <12g/dl. If there is no response after 8 weeks, erythropoietin should be stopped.
- Note that there is an increased thrombotic risk when erythropoietin is used concurrently with IMiDs and corticosteroids. The choice of thromboprophylaxis should reflect this increased risk.

### 8.2 Bleeding – severe thrombocytopenia

Platelets should be transfused when the platelet count <10 x 10<sup>9</sup>/L, or <20 x 10<sup>9</sup>/L in the setting of sepsis. If the patient is bleeding, aim for higher platelet counts, depending on extent and site of blood loss. Consider tranexamic acid in order to maintain haemostasis in patients who have bleeding that is difficult to manage only if the patient is in CR (and if the urine dipstick is negative for blood). For patients receiving low molecular weight heparin, consider the possibility of heparin-induced thrombocytopenia (HIT).

### 8.3 Bleeding – coagulopathy

Coagulopathic states are rare in myeloma but may be associated with dys- or hypo-fibrinogenemia or the development of specific clotting factor inhibitors. Investigation with prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT) and fibrinogen levels should be carried out in the first instance followed by discussion with a specialist haemostasis consultant following detection of specific deficiencies.

### 8.4 Peripheral neuropathy

- Several chemotherapeutic agents for myeloma can be associated with the development of peripheral neuropathy, particularly bortezomib and thalidomide. Development of symptoms is usually associated with cumulative exposure to these drugs but can occur with minimal exposure.
- Symptoms can range from a mild numbness of fingers and toes to severe burning sensation of the extremities. Additionally, symptoms such as tinnitus, visual disturbance, changes in bladder or bowel function, muscle weakness or cramps, erectile dysfunction and decreased ability to sense temperature can all occur.
- Close monitoring of symptoms and appropriate modification of dosing/schedule are critical to prevent the worsening of nerve damage (see individual treatment protocols for dose adjustments).
- Several supportive supplements and reflexology massage have been anecdotally associated with reduction or prevention of neuropathic symptoms. For intractable disease, referral to the pain clinic should be considered.
- The following supplements may be of symptomatic benefit, with bortezomib-associated symptoms:
  - amitriptyline, pregabalin or gabapentin are useful for symptom control
  - Anecdotal evidence for
    - vitamin B group complex strong
    - folic acid 5 mg/d
    - vitamin E – 400iu/d
    - fish oil
    - omega 3 fatty acids
    - evening primrose oil
    - acetyl L-carnitine – 500mg BD
    - alpha lipoic acid – 300mg OD
    - topical cocoa butter
    - topical menthol cream
    - topical capsaicin cream
  - quinine sulphate tablets (for muscle cramps)

## 8.5 magnesium 250mg BD for muscle cramps if magnesium levels are low Radiotherapy

This should always occur following full discussion with clinical oncology colleagues.

Radiotherapy may be required for the following:

- spinal cord or cauda equina compression due to myelomatous deposit:
  - patients should be started immediately on steroids and the patients should follow local treatment pathway for cord compression
  - in addition, patients should be discussed at the myeloma multidisciplinary team (MDT) meeting
  - where appropriate, radiotherapy should be commenced within 24 hours
  - a magnetic resonance imaging (MRI) scan of the whole spine should be performed to enable accurate localisation of the disease to facilitate radiotherapy
  - radiotherapy can be omitted/delayed if the patient is asymptomatic or there has been a complete response to initial steroids or to upfront SACT
- painful bony lesion(s) or extramedullary myelomatous deposit(s) not responding to systemic treatment
- following surgical stabilisation of myelomatous skeletal lesion: radiation should be commenced within 2 weeks if possible and should cover the disease area with a margin.

## 8.6 Pain management

- Pain is one of the most common symptoms experienced by myeloma patients and control is of paramount importance. It is recommended that pain is managed with the support of symptom control/palliative care teams or pain specialists.
- Analgesia: pharmacological pain management is based on an analgesia ladder that includes simple analgesics (paracetamol), weak opiates (co-codamol, tramadol), strong oral opiates (MST, oxycodone) and opiate patches (e.g. fentanyl). Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided in all patients with renal impairment and used in other patients for short durations only (<5 days).
- Amitriptyline, gabapentin and pregabalin are useful for treating neuropathic pain.
- Radiotherapy may be indicated for severe localised pain due to bone infiltration or nerve root compression (see [Radiotherapy, section 8.5](#)).
- Vertebroplasty/kyphoplasty: focal vertebral damage causing persistent pain (e.g. wedge collapse) despite SACT/radiotherapy may be amenable to vertebroplasty/kyphoplasty. These techniques are usually performed by interventional radiologists. A spinal pathway is currently being developed; however, until it is operational, referral to an orthopaedic surgeon with a special interest in myeloma may be appropriate.
- Following orthopaedic advice, the use of bed rest and spinal braces may be appropriate for back pain and improvement of kyphosis for some patients.

## 8.7 Bone disease

- All patients with symptomatic myeloma should receive long-term bisphosphonate therapy regardless of whether bone lesions are present.
- The Myeloma IX study reported that zoledronic acid is superior to sodium clodronate in terms of reduced skeletal-related events and prolonged progression-free and overall survival (6 months advantage) but was associated with an increased risk of osteonecrosis of the jaw (3.5% v 0.3%).<sup>42, 43</sup>
- IV zoledronic acid (4mg monthly over 15/30 minutes) is the bisphosphonate of choice. Dose reduction is recommended if creatinine clearance <60ml/min.
- It is recommended that a dental assessment is carried out prior to treatment initiation with an IV bisphosphonate, with regular dental follow-up and good oral hygiene. Renal function should be carefully monitored with dose reductions in line with manufacturer's guidance.
- Oral calcium and vitamin D supplementation is recommended with zoledronic acid to prevent hypocalcaemia. Any pre-existing vitamin D deficiency should be corrected prior to Zometa initiation.
- The required duration of bisphosphonate therapy has not been defined. However, for patients with no active bone disease and who have had prolonged disease control post treatment (CR), stopping therapy can be considered after 2 years. At the time of disease relapse, bisphosphonate therapy should be reinstituted.
- Patients who require dental extraction whilst on bisphosphonates should be discussed with the tertiary referral centre for expert dental input.
- In some instances, vertebroplasty or kyphoplasty may be appropriate for vertebral fracture/disease for symptom relief. Cases should be discussed with a local radiologist or spinal surgeon.
- Spinal stability is important to assess in all patients to prevent neurological sequelae or future spinal deformity. It is important to look for sternal involvement in those patients with thoracic disease. Cases should be discussed with a spinal surgeon, and consideration of a (C)TLSO brace as appropriate.
- Where appropriate referral to the multidisciplinary team (MDT) and allied healthcare professions should be considered for advice on weight bearing activities and exercise to improve bone health.

## 8.8 Thromboprophylaxis for patients on IMiD drugs

Patients with myeloma who are treated with the IMiD drugs (thalidomide, lenalidomide and pomalidomide) are at an increased risk of venous thrombotic events (e.g. DVT, PE or line thrombosis). The highest period of risk is during the first 4–6 months of therapy. Several factors further increase the VTE rate and include (but are not limited to) a past history of VTE, limited mobility, surgery, obesity, high tumour burden, acute infection, diabetes, chronic renal disease, cardiac disease, concurrent erythropoietin and complex SACT regimens. All patients should have their thrombotic risk assessed and thromboprophylaxis prescribed. Low risk patients should be prescribed aspirin daily. For higher risk patients, low molecular weight heparin (LMWH) or treatment dose warfarin can be used.<sup>3, 44</sup> DOACs have advantages in administration compared with LMWH and fewer drug interactions than warfarin and can be considered for prophylaxis.

Patients with AL amyloidosis and nephrotic syndrome need therapeutic anticoagulation during IMiD-based therapy.

## 8.9 Infections and antimicrobial prophylaxis (also see sections 6.2 and 7.5)

There is an increased tendency towards the development of infections as a result of disease-associated factors such as hypogammaglobulinaemia and treatment-related factors such as neutropenia. There is an increased risk of early infection-related death in myeloma.

- Routine prophylaxis with antibiotics is currently only routinely recommended in the context of induction therapy, with levofloxacin +/- co-trimoxazole.
- Anti-viral prophylaxis is recommended for many patients receiving SACT, including bortezomib-based treatment and stem cell transplant. These patients should receive aciclovir 400mg BD (or 200mg TDS) for a minimum of 3 months post ASCT and bortezomib therapy..
- Routine anti-fungal prophylaxis is not recommended but fluconazole 100mg OD can be considered for those getting steroid containing regimens.
- *Pneumocystis jirovecii* prophylaxis is recommended for patients receiving high dose steroids and should be considered for those receiving bortezomib-based treatment or post-transplant. Options include oral co-trimoxazole 960mg OD Mon/Wed/Fri, dapsone 100mg daily or nebulised pentamidine 300mg monthly.
- Patients should be screened for previous hepatitis B, hepatitis C and human immunodeficiency virus (HIV) infection before starting SACT and before treatment with lenalidomide, pomalidomide and daratumumab. Hepatitis B prophylaxis should be considered if prior hepatitis B infection and should be discussed with the local hepatologist.
- All patients are candidates to receive vaccination against influenza, *Haemophilus influenzae* and *Streptococcus pneumoniae* although responses may be suboptimal. Post-transplant vaccination is also advisable.
- Intravenous immunoglobulins (Ivlg): routine Ivlg is not recommended. However, patients who suffer from recurrent bacterial infections ( $\geq 3$  bacterial infections/year requiring treatment), who have hypogammaglobulinaemia and have failed a trial of prophylactic antibiotics may benefit from monthly infusions of Ivlg (0.5g/kg). Annual review to assess the efficacy of regular Ivlg is required. If the number of recurrent infections has decreased, Ivlg should continue.

## 8.10 Diarrhoea

Therapy with lenalidomide has been associated with onset of diarrhoea reported to be associated with bile acid malabsorption. This can be diagnosed with a SeHCAT scan. This has been reported to respond to reduction in dietary fat content and/or the use of a bile acid sequestrant such as colestevlam (1250 mg TDS) or colestyramine (4g daily TDS). Consider testing levels of fat soluble vitamins to exclude deficiencies. Patients on long term bile acid sequestrants should have triglyceride levels monitored as they may rise, with concurrent risk of pancreatitis<sup>45</sup>

## 9 Treatment Summary and Care Plan

An end of treatment consultation should be offered to every patient. End of treatment is defined for patients with haematological malignancies as when a patient completes systemic anti-cancer treatment (SACT) or changes from intensive induction therapy to ongoing maintenance therapy. Treatment summaries should therefore be agreed when there are any significant changes in treatment and follow-up plans. Holistic Needs Assessments (HNAs) should be offered through follow-up with a care plan completed to document the plans to address any issues raised by the patient.

### 9.1 Treatment summary and care plan

There are two related but distinct documents which patients should be given at the end of treatment:

- A **treatment summary** provides a summary of the cancer treatments received by the end of the first treatment, planned follow-ups (including mechanisms for these), and signs and symptoms of which to be aware. Their aim is to provide information not only to the patient, but also to the GP about the possible consequences of cancer and its treatment, signs of recurrence and other important information.
- A **care plan** is generated as a result of an HNA and is the agreed plan between the patient and healthcare professional about how the identified areas of concern will be addressed. This may cover provision of information (e.g. through an information prescription), onward referral for specialist assessment and intervention (e.g. breathlessness management), or things which the patient themselves can do (e.g. contact their HR department about graduated return to work options).

#### Recommendation

An end of treatment consultation should be offered to every patient. This should include an end of treatment HNA and associated written care plan, and should also include the discussion and provision of a comprehensive treatment summary.

People should be offered access to a health and well-being clinic at the end of treatment. This should provide information to enable the person to self-manage any expected consequences of their cancer and its treatment, as well as general health promotion information, including about diet and physical activity.

The multidisciplinary team (MDT) outcome form and clinic letters will serve to communicate diagnosis, treatment initiation and new lines of treatment to the GP.

## 10 Follow-up arrangements

Patients who have completed SACT will be followed-up regularly (usually every 2–3 months). Myeloma currently remains incurable and follow-up will continue indefinitely, although for patients in long-term remission (>5 years) review every 4–6 months can be considered. Patients will continue to potentially require rapid access to outpatients or acute oncology services and should receive appropriate information regarding contact details in a treatment summary.

Patients with WM on watch and wait should be monitored every 1–5 months depending on clinical status and FBC. Following treatment, follow up should be monthly until count recovery and then 3-monthly.

## 11 Key Worker and Myeloma Clinical Nurse Specialist (CNS)

Haemato-oncology nurse specialists/key workers are trained cancer nurses. Their role is to offer emotional support, information and practical advice from the time of diagnosis throughout the course of treatment and aftercare.

- The CNS should have clinical expertise in identifying, managing and treating complications of disease such as spinal cord compression, renal failure, infections, pain and hypercalcaemia.
- The CNS can provide vital and valuable care and support to other healthcare professionals within the team, both in primary and secondary care.
- The CNS should be present at diagnosis and at any significant discussion of treatment changes and outcomes.
- In the absence of a CNS or key worker, a senior nurse may deputise.
- In the rare case that a CNS or deputy cannot be present, the CNS's contact numbers should be provided. The clinician leading the consultation should advise the CNS, who should then arrange to make contact with the patient.
- The CNS should ensure that all patients are offered a Holistic Needs Assessment (HNA) and associated care plan at key pathway points including within 31 days of diagnosis, at the end of each treatment regime and whenever a person requests an assessment. The care plan should be developed with the patient following discussion of their concerns as identified on the HNA and be documented in their notes, with onward referral made to appropriate healthcare and allied health professions. Patients will require ongoing assessment and evaluation throughout the course of their disease and the CNS will have a pivotal role in caring for and supporting patients using expert knowledge of the pathophysiology of myeloma and treatment regimens.
- All patients should have a card documenting the CNS/key worker's name and contact details, together with an out-of-hours contact for urgent advice.



## 12 Clinical Trials and Biobanking

All patients should be considered for trial entry where appropriate and consideration should be given to referring a patient to a specialist centre where a suitable trial may be open.

London hospitals will support the National Cancer Research Institute (NCRI) and Myeloma UK clinical trial portfolios as well as participating in commercial studies investigating novel myeloma agents if appropriate.

Several London hospitals will maintain suitable trials for patients in the following categories:

- presenting younger fitter patients
- presenting older less fit patients
- frail patients
- 1–3 prior therapies
- relapsed and refractory patients.

Biobanking is a particularly important aspect of research and all patients should be offered the opportunity to provide samples to the biobank.

## 13 End-of-life Care

Discussion about preferred priorities for care and advanced care planning should be initiated if it is thought likely that the person will die within a year.

Where appropriate, discussions about prognosis and treatment options should also include discussions about end-of-life care, preferred place of end-of-life care and the use of do not resuscitate orders. These are to facilitate transitions between active disease-modifying therapy to supportive care only at the time of disease progression/non-response. Care may be required from specialist palliative care teams.

Members of the myeloma team, the named CNS/key worker, the patient, family members and symptom control/palliative care teams may be involved. Clear documentation of the discussion with guidance to the treating teams is helpful in communicating these discussions and outputs to the GP and the wider team that may be more involved in the management and care of the individual.

## 14 Data Requirements

Accurate data collection is essential to monitor outcomes, and the collection of this information, particularly clinical data, remains the responsibility of the members of the multidisciplinary team with support from a data manager. Haematology services are required to submit data to nationally mandated datasets for all patients diagnosed with haematological cancer; further details on these datasets are available in [Annex 3](#)).



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The British Committee for Standards in Haematology (BCSH) in collaboration with the UK Myeloma Forum (UKMF) has issued comprehensive guidelines for the investigation, diagnosis, clinical management and supportive care of multiple myeloma. Additionally, guidelines are available for the management of monoclonal gammopathy of undetermined significance (MGUS), solitary plasmacytoma of the bone, extramedullary plasmacytoma, and AL amyloidosis from the BSH guidelines website ([www.b-s-h.org.uk/guidelines](http://www.b-s-h.org.uk/guidelines)).

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## Annex 1: SACT Regimens

| Single                  | Double                         | Triplet                         | Combinations         |
|-------------------------|--------------------------------|---------------------------------|----------------------|
| Methylprednisolone      | MP                             | CVAD or CVAMP                   | TIDE                 |
| Dexamethasone HD        | TD                             | TAD                             | ABCM                 |
| Dexamethasone LD        | RD                             | RAD                             | CVTD                 |
| Melphalan               | PD                             | CTD and CTDa                    | CVRD                 |
| Cyclophosphamide weekly | VD twice weekly or once weekly | CRD                             | Carf/Cyclo/Rev/Dex   |
| Cyclophosphamide daily  | Car/Dex                        | CVD twice weekly or once weekly | DT-PACE              |
| Etoposide LD            | Len/Vorinostat                 | PAD                             | VDT-PACE             |
| Carmustine CCNU         | Len/Vel                        | PCD                             | VDT/Carbo/ACE        |
| Bendamustine            | Benda Dex                      | Car/Cyclo/Dex                   | PACE                 |
| Thalidomide             | ZDex                           | MPT                             | Split dose melphalan |
| Lenalidomide (full)     |                                | MPR                             | Tandem transplant    |
| Lenalidomide (10mg)     |                                | Pom/Car/Dex                     | Allo low dose TBI    |
| Pomalidomide            |                                | Benda TD                        | CiDEx                |
| Bortezomib (1,4,8,11)   |                                | Benda VD                        | CEP                  |
| Bortezomib weekly       |                                | VTD                             | ESHAP                |
| Vorinostat              |                                | VRD                             | DCEP                 |
| Carfilzomib             |                                | PVD                             |                      |
| High dose melphalan     |                                | Vorinostat/Vel/Dex              |                      |
| Vemurafenib             |                                | VMP                             |                      |

## Annex 2: Minimum Dataset to be Stored at Presentation and Relapse (in line with COSD)

|                                      |          |              |        |
|--------------------------------------|----------|--------------|--------|
| Data point                           |          |              |        |
| Age (years)                          |          |              |        |
| Performance status (ECOG)            |          |              |        |
| Haemoglobin level (g/L)              |          |              |        |
| White cell count ( $\times 10^9/L$ ) |          |              |        |
| Platelet count ( $\times 10^9/L$ )   |          |              |        |
| Creatinine (mmol/L)                  |          |              |        |
| B2M (mg/L)                           |          |              |        |
| LDH (iu/L)                           |          |              |        |
| CRP (mg/L)                           |          |              |        |
| Albumin (g/L)                        |          |              |        |
| ISS stage                            |          |              |        |
| Bone disease                         | None     | Intermediate | Severe |
| Calcium level (mmol/L)               |          |              |        |
| Plasma cells percentage aspirate     |          |              |        |
| Plasma cell percentage trephine      |          |              |        |
| Molecular/iFISH                      | 1p-      | Y / N        |        |
|                                      | 17p-     | Y / N        |        |
|                                      | 1q+      | Y / N        |        |
|                                      | t(4;14)  | Y / N        |        |
|                                      | t(11;14) | Y / N        |        |
|                                      | t(14;16) | Y / N        |        |
|                                      | t(14;20) | Y / N        |        |
| Presence of extramedullary disease   | Y / N    |              |        |
| Peripheral blood plasma cells        | Y / N    |              |        |

## Annex 3: Data Requirements

Haemato-oncology services within London are required to submit data to the following nationally mandated datasets for all patients diagnosed with haematological cancers.

### The Cancer Outcomes and Services Dataset (COSD)

The core dataset for all tumour types including haematological cancers is mandated from January 2013, and the site-specific dataset is mandated from July 2013. Details of the dataset can be found on the National Cancer Intelligence Network website:

[www.ncin.org.uk/collecting\\_and\\_using\\_data/data\\_collection/cosd.aspx](http://www.ncin.org.uk/collecting_and_using_data/data_collection/cosd.aspx)

The local cancer registry will be collating this dataset using Trust data feeds which should include all these items. The feeds are:

- Trust PAS
- Trust pathology
- Trust radiology
- Trust multidisciplinary team (MDT) feed.

In line with the requirements set out in Provider Trust contracts, this data should be submitted within 25 working days of the end of the month in which the activity took place.

Three groups of haematological cancers are considered stageable by the Registry:

- Lymphomas, using Ann Arbor (or Murphy St Jude for children)
- Myelomas, using ISS
- CLLs, using Rai and Binet

For the purposes of COSD, any other haematological cancers are not counted as stageable.

**For CLL both Rai (0-IV) and Binet (A-C) stages need to be recorded and submitted to COSD to be considered “fully staged”.**

**MGUS does not need to be recorded and submitted as it is not defined as an invasive tumour.**

### Systemic Anti-Cancer Therapy dataset (SACT)

Provider Trusts that provide chemotherapy to patients are required to submit data to the SACT dataset. Details of the audit and the dataset requirements are available on the dataset homepage:

[www.chemodataset.nhs.uk/home.aspx](http://www.chemodataset.nhs.uk/home.aspx)

### Radiotherapy Dataset (RTDS)

Provider Trusts that provide radiotherapy to patients are required to submit data to the RTDS dataset. Details of the audit and the dataset requirements are available on the dataset homepage:

[http://www.ncin.org.uk/collecting\\_and\\_using\\_data/rtds](http://www.ncin.org.uk/collecting_and_using_data/rtds).

## Cancer Waiting Times dataset

Trusts are required to submit data to the Cancer Waiting Times dataset, which includes details of all patients who are referred as a 2 week wait (2ww) referral, and all patients who are treated for cancer. Trusts are required to submit this data within 25 working days of the month of either when the patient was first seen for the 2ww target, or when the patient was treated. The cancer waiting times dataset can be found at:

[www.datadictionary.nhs.uk/data\\_dictionary/messages/clinical\\_data\\_sets/data\\_sets/national\\_cancer\\_waiting\\_times\\_monitoring\\_data\\_set\\_fr.asp](http://www.datadictionary.nhs.uk/data_dictionary/messages/clinical_data_sets/data_sets/national_cancer_waiting_times_monitoring_data_set_fr.asp)



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