LONDON CANCER ALLIANCE
West and South

LCA Haemato-Oncology Clinical Guidelines

Plasma Cell Disorders

April 2015

Contents

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, POEMS syndrome and Waldenström's macroglobulinemia.

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),[1–3] MGUS,[1] plasmacytoma[4] and AL amyloidosis.[5, 6] These LCA 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 a number of 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 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 ~1% of all cancers.[7] 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 4,500 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,[7, 8] 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. The International Myeloma Working Group has recently recommended initiating myeloma systematic anti-cancer treatment (SACT) for those patients with smouldering disease at highest risk for early progression.[9]

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 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 κ/λ 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.[1] In contrast, in renal disease and in the case of polyclonal B-cell activation there may be increased levels of both κ and λ 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).[10]

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.[11]

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 and monoclonal immunoglobulin deposition disease

These rare disorders are characterised by the deposition of light chains or intact monoclonal immunoglobulin deposition in a range of organs. 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.

1.7. Waldenström's macroglobulinemia

Waldenström's macroglobulinemia (WM) is classified as a lymphoplasmacytic lymphoma (LPL) by the World Health Organization and REAL classifications. It is an indolent B-cell lymphoproliferative disorder with an age adjusted incidence of 0.55 per 100,000. Median age at diagnosis is 73 years with a male predominance.

Symptoms and signs are classically related to bone marrow infiltration of lymphoplasmacytoid cells (normocytic anaemia, cytopenias) and IgM paraproteinemia (hyperviscosity, neuropathy, cryoglobulinemia, cold agglutinin disease, rarely amyloidosis). Lymphadenopathy, organomegaly and extranodal masses can also be a presenting feature.

2. Early Diagnosis and Prevention

Myeloma often presents late due to a failure to recognise symptoms. Patients with persistent back pain for longer than 4–6 weeks with no obvious trigger should have an FBC, ESR and immunoglobulin profile as well as a spinal x-ray as a minimum. 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 may be appropriate for patients with very high paraprotein/light chains, significant anaemia, hypercalcaemia, bone lesions or renal failure to be referred via the 2 week wait pathway (See Appendix 1: 2 Week Wait Referral Forms).

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. A joint approach with elderly care physicians, renal physicians, neurologists and palliative care teams may be appropriate.

All cases with ultra-high risk disease destined for intensive treatment should be identified, discussed frequently and early with the myeloma team and transplant centre and, where appropriate, be treated at the transplant centre.

2.1.1. Service configuration and MDTs across the LCA

All patients with a new diagnosis of a plasma cell disorder (including monoclonal gammopathy of undetermined significance/MGUS) should be discussed at a myeloma 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 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. For details of JACIE-accredited transplant centres in the LCA and contact details please see Annex 1.

Some MDTs hold a separate myeloma meeting and others discuss patients with myeloma as part of their haematology MDT. For details of MDTs across the LCA please see Annex 2.

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), serum protein electrophoresis (SPEP) and serum free light chains; urine for Bence Jones protein and albumin; creatinine ratio
- bone marrow aspirate and trephine histology
- bone marrow aspirate immunophenotyping, if relevant
- cytogenetic status
- specific diagnosis/category of plasma cell disorder
- relevant imaging
- risk score (at least International Staging System/ISS)
- availability of a clinical trial/research study and 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 (email, fax preferably) within 24 hours of MDT discussion.

3. Investigation and Diagnosis

Myeloma often presents late due to a failure to recognise symptoms. Patients with persistent back pain for longer than 4–6 weeks with no obvious trigger should have a full blood count (FBC), erythrocyte sedimentation rate (ESR) and immunoglobulin profile as well as a spinal X-ray as a minimum. 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.

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

Patients with the following clinical problems should be investigated for evidence of underlying plasma cell disorder:

- serum or urine monoclonal protein
- abnormal serum free light chain ratio
- presence of lytic lesions on radiological imaging
- cast nephropathy/amyloid/light chain deposition on renal biopsy
- evidence of amyloid infiltration or light chain deposition in other organs
- unexplained raised ESR
- unexplained immunoparesis
- circulating plasma cells on blood film or on flow cytometry
- diagnosis of plasmacytoma on biopsy
- unexplained hypercalcaemia
- unexplained hyperviscosity
- unexplained anaemia (normocytic or macrocytic)
- unexplained persistent bone pain (for more than 4 – 6 weeks), especially axial skeleton
- unexplained proteinuria (nephrolic range)

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
- 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:

- FBC
- plasma viscosity (if available)
- renal function (creatinine, estimated glomerular filtration rate/eGFR) and electrolytes (urea and electrolytes/U&E; MDRD estimation of GFR is preferred)
- liver function tests (LFTs)
- serum albumin, corrected serum calcium
- uric acid
- serum protein electrophoresis (SPEP), immunofixation and paraprotein quantitation
- serum immunoglobulins
- serum free light chain (SFLC) levels and ratio
- beta-2 microglobulin (B2M)
- C-reactive protein (CRP)
- lactate dehydrogenase (LDH)
- serum vitamin B12 and folate
- coagulation screen (prothrombin time/PT; activated partial thromboplastin time/APTT; fibrinogen)
- blood film and flow cytometry for circulating plasma cells, if appropriate
- virology screening if systemic anti-cancer treatment (SACT) is required (hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, human immunodeficiency virus/HIV antigen/antibody).

3.1.3. Urinalysis

- All patients should be screened for urinary Bence Jones protein and excess urine protein loss
- Urine electrophoresis (Bence Jones protein) including immunofixation and quantitation (preferably 24-hour urine)
- 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 with a paraprotein >10-15g/L or an involved: uninvolved free light chain ratio >10 (SFLC ratio greater than 8 is associated with 40% risk of progression to myeloma at 2 years) 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
  - molecular (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 which 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-
  - 1q+
- GEP (extended panel of investigation if available).

3.3. Imaging investigations

Imaging of the skeleton is indicated for all patients with a significant serum paraprotein (>10g/L) or abnormal SFL ratio (>8) or low level paraprotein (<10 g/L) with bone pain or clinical suspicion. It is also indicated for patients with bone marrow plasma cell percentage >10%. In line with recent IMWG recommendations, patients with asymptomatic myeloma require more detailed MRI imaging to identify focal lesions.[9]

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.[12, 13] Significant advances in imaging technologies have paralleled developments in therapy for myeloma. Local availability will determine the imaging investigation undertaken.

A number of imaging investigations (listed below in order of availability within the NHS) provide important clinical information:

- **Skeletal survey:** Standard x-rays of the skeleton including AP and lateral cervical spinal, thoracic and lumbar spine, skull, chest, pelvis, humeri and femora. This is available throughout the NHS and suitable for the diagnosis for myeloma. However, note that a negative skeletal survey does not rule out myeloma or active bone disease. It has a sensitivity of 30% versus CT/MRI of 80% for osteolytic bone disease.
- **Low dose whole body CT** (skull base to thighs) is an alternative where facilities exist with supplementary skull and rib plain films where this is clinically relevant (e.g. to assess site specific symptoms or if no lesions are detected elsewhere on CT. This is more sensitive than skeletal survey and can replace this where local expertise is available. It has the advantage of demonstrating extraosseus sites of disease (Grade B recommendation; Level III evidence).
- **Limited MRI scan of the spine and bony pelvis** is for suspected spinal cord or nerve root compression. This also has a role for assessment of bone pain where there is a negative skeletal survey and can be used where whole body MRI is not possible (Grade B, Level IIB evidence)
- **Whole body MRI** including diffusion weighted sequences is a highly sensitive method to demonstrate the presence of focal bone lesions, distribution of marrow disease and extraosseus disease. This is recommended where there is local expertise. (Grade B, Level IIA evidence).
- **Whole body PET-CT scan** can detect focal lesions, extramedullary disease and potentially demonstrate disease response post treatment efficiently (Grade B recommendation, Level II evidence)

Bone scanning has no place in the routine staging of patients with myeloma.

Urgent CT may be used to establish the presence of suspected cord compression in cases where MR imaging is unavailable, impossible due to patient intolerance or contraindicated e.g. intraorbital metallic foreign bodies or cardiac pacemakers (Grade B recommendation; level III evidence).

CT of the spine may be considered to clarify the presence or absence of bone destruction in cases of clinical concern where MRI is negative (Grade B recommendation; level III evidence).

CT or MRI should be used to clarify the significance of ambiguous plain radiographic findings, such as equivocal lytic lesions, especially in parts of the skeleton that are difficult to visualise on plain radiographs, such as ribs, sternum and scapulae (Grade B recommendation; Level III evidence).

CT is indicated to delineate the nature and extent of soft tissue disease, and where appropriate, tissue biopsy may be guided by CT scanning (Grade B recommendation; Level IIB evidence).

MRI should be performed to stage solitary plasmacytoma, to exclude other occult sites of disease (Grade B recommendation, Level IIIB evidence). MRI has a role in evaluating patients with non-secretory disease as it is highly sensitive.

PET-CT can be used to determine disease extent in selected patients with myeloma and to evaluate patients with non-secretory disease. It has prognostic value at staging but MRI may be preferred as it is more sensitive for disease detection (Grade B recommendation, Level III evidence).

PET-CT can detect response early and may have a future role in trials to assess new agents or risk adapted therapies (Grade B recommendation, Level IIA evidence). PET-CT may give prognostic information in patients suitable for ASCT. (Grade B recommendation, Level IIB evidence). PET-CT may also be used to confirm solitary plasmacytoma and exclude other sites of occult disease.

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, NT-pro-BNP, troponin T (for amyloid staging)
- renal/liver ultrasound
- cardiac MRI
- serum amyloid P (SAP) scan (at NAC, RFH)
- upper and lower gastrointestinal assessment by endoscopy
- autonomic function tests
- consider cardiac biopsy if MRI non-diagnostic.

3.4.2. For suspected POEMS syndrome

- endocrine assessment
- testosterone, oestradiol
- fasting glucose, glycosylated haemoglobin
- thyroid stimulating hormone (TSH), parathyroid hormone (PTH), prolactin, cortisol

- luteinising hormone (LH), follicle-stimulating hormone (FSH), adrenocorticotropic hormone (ACTH)
- ultrasound or CT abdomen to determine organomegaly
- vascular endothelial growth factor (VEGF) levels where available.
- lung function
- nerve conduction studies
- skeletal survey for evidence of osteosclerotic lesions.

3.4.3. Waldenström's macroglobulinemia

Evaluation at presentation

- ECOG performance status
- B symptoms
- symptoms suggestive of hyperviscosity, neuropathy, cryoglobulinemia and cold agglutinin disease
- physical examination for lymphadenopathy and organomegaly
- fundoscopy to look for venous engorgement ('sausaging') as a sign of clinically relevant hyperviscosity
- FBC
- further tests performed at diagnosis include: biochemistry (including albumin, bone profile and urate), ferritin, transferrin saturation, LDH, B2M, Igs, serum protein electrophoresis and immunofixation, serum free light chains , Bence Jones proteins and hepatitis B, C and HIV serology
- plasma viscosity if signs/symptoms or IgM >30g/L
- cryoglobulins (EDTA sample at 37°C) where appropriate
- bone marrow aspirate and trephine, immunohistochemistry – bone marrow sample for immunophenotyping, FISH analysis and molecular studies for MYD 88 and CXCR4 mutations
- neck/chest/abo/pelvis CT scan
- PET-CT may be useful if high grade transformation is suspected
- lymph node or tissue biopsy where appropriate.

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 (see Annex 8 for list of SIHMDS or current diagnostic services and contacts).

BMAT:

Slides for morphology to SIHMDS lab

2–5ml in EDTA for immunophenotyping with a slide

2–5ml in EDTA for molecular genetics

2–5ml in heparin (PFH or lithium heparin) for cytogenetics/FISH, trephine for histopathology

4. Diagnostic Criteria

4.1. Diagnostic criteria for symptomatic multiple myeloma

- Monoclonal plasma cells in bone marrow (aspirate or trephine) ≥10%
- Serum paraprotein ≥30g/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 Ca2+>0.25mmol/L above normal or >2.75mmol/L)
  - **R**: renal impairment (no other cause)
  - **A**: anaemia (Hb <100g/L or <20g below normal) not due to other causes
  - **B**: bone lesions (lytic lesions or osteoporosis).

Additionally recent IMWG guidance recommends treatment for patients without CRAB features but one of the following:[9]

- bone marrow plasma cell percentage ≥ 60%
- serum free light chain ratio (involved/uninvolved) ≥ 100
- more than one focal bone lesion on MRI studies.

4.2. Diagnostic criteria for smouldering asymptomatic myeloma

- Monoclonal serum protein of >30 g/L **and/or**
- 10–60% or more clonal plasma cells in bone marrow
- Absence of end organ damage defined by CRAB or IMWG defined biomarkers of malignancy.

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

- Paraprotein <30 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 <500mg/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 and light chain deposition disease

- 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)
- Absence of significant bone marrow plasma cell infiltrate (<10%)
- Absence or presence of monoclonal serum or urine protein (if amyloid is present it is important to distinguish whether patients also have myeloma; if myeloma is present then patients should be treated according to this pathway).

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.[11]

- Mandatory major criteria:
  - presence of monoclonal plasma cell disorder (e.g. serum paraprotein, usually λ 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.

4.8. Diagnostic criteria for WM

There are no uniform diagnostic criteria but the most widely used are:

- BM infiltration with small lymphocytes, plasmacytoid cells and plasma cells accounting for > 30% of nucleated cells, with the following immunophenotype: sIg^+ (5:1 κ:λ ratio) $CD19^+$ $CD20^+$ $CD23^-$ $CD5^-$ CD10.
- Presence of monoclonal IgM > 30 g/L. (IgG, IgA and non-secretory WM accounts for <5% of cases).
- **Immunophenotype of WM:** B cell associated antigens: CD19, CD20, CD22, CD79A. Surface and/or cytoplasmic Ig (usually IgM). CD5 is expressed in 5–20% of cases. CD23 may be expressed in 10–35% of cases.
- Genetic characteristics of WM:
  - The commonest cytogenetic abnormality (>50% of cases) is 6q21 (BLIMP-1)-. Other abnormalities that have been described include trisomy of chromosomes 4, 5 or 8 and 20q-.
  - MYD88 (L265P) is a commonly recurring mutation found in >90% of LPL. Allele-specific PCR may be useful for differentiating WM from other lymphoid neoplasms in difficult cases.
  - CXCR4 mutation is present in 30% of patients.
  - 17p13 (TP53) deletion or 14q32 (IGH) translocations in <10% of patients and are associated with shorter progression-free survival.
- Absence of lytic lesions and mature plasma cell infiltration to distinguish WM from IgM myeloma.

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:[14]

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

Table 5.1: The International Staging System

Stage	Criteria	Median survival
I	Serum ß2m <3.5mg/L and serum albumin ≥35g/L	62 months
II	Neither I nor III	45 months
III	Serum ß2m ≥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.[15–17]

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%
BRAF	Response to BRAF inhibition	4%

5.1.3. Combined ISS/genetic risk groups

A number of groups have now defined risk groups based on ISS stage and FISH abnormalities, including UK Myeloma IX data.[17] These risk groups are defined in Table 5.3.

Table 5.3: Defined risk groups

Risk group	Group
Standard risk	The rest
Intermediate risk	One of: t(4;14), t(14;16), t(14;20), 17p-, 1q+, 1p- and β2m <5.5 or blastic morphology
High risk	One of: t(4;14), t(14;16), t(14;20), 17p-, 1q+, 1p- and β2m ≥5.5
Ultra-high risk	More than one of: t(4;14), t(14;16), t(14;20), 17p-, 1q+, 1p- or GEP of high risk disease or plasma cell leukaemia

5.1.4. Monitoring myeloma patients for prognostic variables

- Patients should be seen 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.
- Repeat β_2-microglobulin at relapse prior to starting a new therapy.
- Annual diffusion-weighted magnetic resonance imaging (MRI) can be done if available.

5.2. Asymptomatic/smouldering myeloma

The probability of progression to symptomatic MM requiring treatment is 51% at five years (10%/year for first 5 years), 66% at 10 years (3%/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 that 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%≥60%, involved: uninvolved SFL ratio ≥100 (with involved light chain level ≥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.[9]

5.2.1. Risk stratifying asymptomatic myeloma

A number of 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[18]

Risk group		Absolute risk of progression at 10 years, %	Absolute risk of progression at 10 years accounting for death as a competing risk, %
High risk	(Paraprotein ≥30g/L and BMPCs >10%)		
	FLC ratio: 0.125 – 8	58.8	51.3
	FLC ratio: <0.125 or >8	83.8	75.2
Intermediate risk	(Paraprotein < 30g/L and BMPCs >10%)		
	FLC ratio: 0.125 – 8	58.3	40.4
	FLC ratio: <0.125 or >8	68.5	56.8
Low risk	(Paraprotein ≥30g/L and BMPCs <10%)		
	FLC ratio: 0.125 – 8	32.2	22.8
	FLC ratio: <0.125 or >8	33.3	25.0

Table 5.5: The Spanish SMM risk stratification system[19]

High risk	Flow cytometry: ≥ 95% of plasma cells are clonal **or** hypogammaglobulinemia **or** evolving patients
Low risk	All other patients

Additionally, a number of biomarkers have potential early predictive ability for the transformation of smouldering/asymptomatic myeloma to symptomatic disease. This includes increase in serum monoclonal protein by ≥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.[20]

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

- paraprotein ≥15g/L
- non-IgG isotype
- abnormal SFLC ratio (<0.26 or >1.65mg/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, %
Low risk (no factors present)	5	2
Low–intermediate risk (any 1 factor present)	21	10
Intermediate risk (any 2 factors present)	37	18
High risk (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.[21] 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.[22] 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%.[9]

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.[9]

Table 5.7: Risk stratification

Risk group	Variables	5-year progression rate
Low	Normal SFLC ratio Paraprotein <5 g/	13%
Intermediate	Either variable abnormal	26%
High	Abnormal SFLC ratio Paraprotein ≥5g/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.[5] The Mayo Clinic has recently updated its prognostic scoring model which utilises Troponin T, NT-pro BNP and SFL to identify four prognostic groups.[23]

A score of 1 is assigned for each prognostic variable: Cardiac Troponin T >=0.025 ng/ml, NT pro-BNP >=1800 pg/ml, difference in involved and uninvolved SFL (dSFL) >=180mg/L, and the total score is used to assign a prognostic stage. 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
0	94 months	64 – 154
1	40 months	24 – 59
2	14 months	11 – 18
3	5.8 months	5 – 7

5.6. Risk stratification for WM

5.6.1. Prognosis

- **IPSSWM (**International Prognostic Scoring system for WM)

Risk factors
Age >65yrs
B2M >3mg/L
M-protein>70g/L
Hb≤11.5g/L
Plts<100 x 10^9/L

Risk group	Score	5yr OS
Low risk 27%	≤1 risk factor and age ≤65	87%
Intermediate risk 38%	2 risk factors or age >65	68%
High risk 35%	>2 risk factors	36%

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
- pre-transplant consolidation
- 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)
- whether they are standard, high or ultra-high risk as defined in these guidelines.

SACT may also be indicated for the management of high risk smouldering myeloma.

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 BCSH *Guidelines for supportive care in multiple myeloma*.

- 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 commending bisphosphonates.
- For all treatment regimens dose reduction should be avoided and dose intensity maintained using GCSF.
- 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
  - Azole prophylaxsis may be considered in regimens containing high-dose steriods

  - Co-trimoxazole is required for all ASCT patients and all patients recovering from intensive SACT e.g. VTD-PACE.
- 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 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 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 mobilisation.

Following high dose therapy and when off treatment

- Serum and urine paraproteins or SFLC at two-monthly intervals
- Full blood count (FBC) and urea and electrolytes (U&E)
- Bone marrow assessment at three 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[24] 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 resistant disease if a patient is in CR is important in order to define stringent CR which is an important end point and indicator of outcome.
- 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

Complete remission (CR)	Negative immunofixation on serum and urine Disappearance of any soft tissue plasmacytomas <5% plasma cells in bone marrow
Stringent complete remission (sCR)	As above and: Normal SFLC ratio and no evidence of clonal plasma cells on immunohistochemistry or flow cytometry
Very good partial response (VGPR)	>90% reduction in serum paraprotein and <100mg/24h BJP
Partial response (PR)	>50% reduction in serum paraprotein and/or >90% reduction in BJP and/or ≥50% decrease in difference between involved and uninvolved SFLC and/or >50% decrease in bone marrow plasma cells (if non-secretory multiple myeloma)
Stable disease/no response (SD)	None of the above and not progressive disease Define the time to progression
Progressive disease (PD)	>25% increase in serum paraprotein (absolute increase >5g/L) Urinary BJP (absolute increase >200mg/24h) Difference between SFLC (absolute increase >100mg/L) Bone marrow plasma cells (absolute >10%) New bone lesions/plasmacytomas Myeloma-related hypercalcaemia
Primary refractory	Defined as having never achieved partial response on therapy (PR) Non-responding, non-progressive Progressive disease
Relapsed/refractory	Achieved partial response on therapy (PR) then progressed within 60 days
Relapsed	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 a number of features including age, disease subtype and performance status.

The important clinical subtypes of myeloma are laid out below:

- transplant eligible
- ultra-high risk disease
- plasma cell leukaemia
- transplant non-eligible
- severe renal failure
- solitary plasmacytoma
- multiple solitary plasmacytoma
- extramedullary plasmacytoma.

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

For elderly patients, disease stability and lack of symptoms are important considerations.

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 3.

All patients should be considered for entry into a clinical trial at each of their disease stages.

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 a number of 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.
- For non-clinic trial entry, bortezomib based-therapy (such as VTD/CVD) can be used.[25, 26] CTD can be considered if bortezomib administration is not appropriate or acceptable to the patient.[27]
- Doublets are generally less effective than triplets.
- Bortezomib-based triplets and combinations such as CVD, VTD and VDT-PACE are indicated for patients with ultra-high risk disease.

- Combination of cytotoxic agents with novel therapies may be appropriate in some settings such as ultra-high risk disease.

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).
- 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 x 10^6 CD34+ cells/kg is required to undergo autologous transplant. However, 5 x 10^6 CD34+ cells/kg is the preferred target for collection.
- A patient may undergo two autografts and the minimum target should be at least 5 x 10^6 CD34+ cells/kg aiming for 10 x 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 (200mg/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 >12–18 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^2 is recommended although a dose reduction based on glomerular filtration rate (GFR) or age/co-morbidities may be required.
- 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 BSCH guidelines on amyloidosis.

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.[28, 29] Tandem ASCT can be used in appropriate settings.

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
- Dose reduction based on creatinine clearance should be considered
- 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 LCA transplant guidelines.

e) Post-transplant consolidation

A number of clinical trials demonstrate that:[30]

- 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[31]
- alkylating agents should be avoided post-ASCT
- bortezomib, if used for induction, may also be have benefit when used post-transplant.

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.[30, 32]
- 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 in this setting but is not licensed. Two large studies have been performed which are associated with improved progression-free survival in both studies and overall survival in one study.[33, 34]

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

g) Ultra-high risk disease in TE patients

Ultra-high risk patients have a particularly poor outcome and can be treated intensively where clinically appropriate with the aim of maximising initial response 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
- bortezomib and lenalidomide maintenance should be considered.

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 x 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 VTD35.

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.

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

Based on clinical trial evidence, treatment with bortezomib/alkylator/corticosteroid (e.g. VMP) is recommended as first-line therapy.[36, 37] An alternative is CVD.

For patients who are unable to attend hospital regularly or for whom oral therapy is considered more appropriate, MPT or CTDa are a suitable alternative27.[38]

While recent trial data (e.g. the MM020 study) suggest a possible role for lenalidomide-based therapy, it is not currently licensed and is not funded by the National Institute for Health and Care Excellence (NICE)/NHS England.[39]

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.[30]

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.[40] However, it should be noted that it is currently neither licensed nor NICE approved for this indication.

6.5.1.3. Patients with severe renal failure

Up to 30% of newly diagnosed patients present with evidence of renal impairment (creatinine >200µmol/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.
- 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.[41]

- Bortezomib, thalidomide and dexamethasone combinations are appropriate in this setting and do not require 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.[26]
- For patients for whom salvage of renal function remains a possibility, regular SFL should be monitored (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 <40ml/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 <10ml/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 higher. Close liaison between the renal and transplant teams is essential.

6.5.2. Primary relapsed and refractory disease

The strict definition of relapsed and refractory myeloma, as defined by the IMWG, is disease that is non-responsive while on salvage therapy, or progresses within 60 days of the last therapy in patients who have achieved minimal response or better at some point previously before then progressing in their disease course.

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 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.

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 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 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.

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.
- If a long PFS is seen with a treatment it may be appropriate to use it again at relapse.
- If a short PFS was seen with a treatment, or the rate of relapse is rapid, swapping to a therapy with different mechanisms of action is appropriate.
- Relapse on ongoing treatment is a special situation and needs to be managed appropriately.

First relapse

- The aim is to maximise response and prolong progression-free survival.
- Bortezomib-based regimens are recommended by NICE in this setting.
- 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 12–18 months, or ASCT was not used at first response.
- If bortezomib is contraindicated, lenalidomide is a good alternative.

- If bortezomib was used at presentation and the patient had a good response, rechallenge with bortezomib may be appropriate. If the response to first-line bortezomib was inadequate or associated with unacceptable toxicity, lenalidomide should be used (funded via the NCDF).

Second relapse

- Lenalidomide is indicated by NICE at second relapse.
- Triplets such as CRD are more effective than doublets such as RD.
- 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.
- Autologous transplant as consolidation can be considered provided the patient is medically fit and first transplant progression-free survival was longer than 12–18 months, or ASCT was not used at previous response.

Third and subsequent relapse

- Pomalidomide combinations can be used via the NCDF.
- Bendamustine combinations can be used via the NCDF.
- Use other novel combinations including VTD and VRD.
- Use conventional chemotherapy combinations such as intermediate dose melphalan.
- Carfilzomib has activity in this setting. (Not NHS funded)
- Patients should be entered into clinical trials.

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.
- Patients will be reviewed following treatment in the MDT meeting to allow the response assessment to be formally recorded.

6.5.3. Multiple solitary plasmacytomata of bone

- In many instances it is appropriate to treat patients with multiple plasmacytomata as myeloma.
- This rare situation requires specific MDT discussion.

6.5.4. 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.

6.6. Systemic anti-cancer treatment (SACT) for Waldenström's macroglobulinaemia

For asymptomatic or "smouldering" WM as with other indolent lymphoproliferative disorders, a watch and wait approach is indicated.

Indications for treatment are as follows:

- hyperviscosity
- B symptoms
- cytopenias
- symptomatic adenopathy/organomegaly
- cryoglobulinemia
- cold agglutinin disease
- neuropathy
- amyloidosis

Wherever possible patients should be entered into clinical trials.

Factors to take into account when symptomatic disease and treatment initiation: ECOG performance status, age, co-morbidities, cytopenias, hyperviscosity symptoms and need for rapid symptom control, bulky disease, symptomatic peripheral neuropathy and eligibility for high dose therapy and stem cell transplantation. Response to treatment is assessed as per the consensus guidelines from the international workshop on WM (see Annex 5). The currently used regimens are listed in Annex 6.

- Patients >65yrs/high dose therapy ineligible: First line therapy
  - Chlorambucil +/- prednisolone +/- rituximab may be appropriate for older, frailer patients.
  - Dexamethasone/rituximab/cyclophosphamide (DRC) can be offered to patients with cytopenias.
  - Fludarabine or cladiribine +/- rituximab +/- cyclophosphamide. Prolonged lymphopenia and higher risk of infections from purine analogues should be borne in mind.
  - Single agent rituximab weekly x4 is an option for patients who cannot tolerate chemotherapy. It is important to remember that patients with a high IgM may require prior plasmapheresis due to the risk of 'IgM flare' following rituximab administration.
  - R-Bendamustine may be preferable in the setting of neuropathy
- Patients <65yrs / high dose therapy eligible: First line therapy
  - R-CHOP can be considered for bulky disease
  - R-bendamustine may be preferable in the setting of neuropathy
  - R-bortezomib +/- dexamethasone can be useful to reduce paraprotein load quickly in the setting of hyperviscosity.
  - DRC
- Relapsed/refractory disease

  Management of relapse and refractory WM disease depends on the time of relapse, the type and number of previous therapies, the ECOG performance status, age and patient co-morbidities at relapse and the nature of relapse. In patients who maintain a response >1year after cessation of their

1st line treatment, it may be reasonable to repeat the same regimen. If high dose therapy is planned, avoid purine analogues as these may affect stem cell collection.

  - Bortezomib can be used (with rituximab) in patients who have received prior therapy with alkylating agents and purine analogues (CDF 2014)
  - Autologous stem cell transplant may be considered in patients who relapse <12 months or have an aggressive clinical course but achieve a CR/PR with <10% lymphocytosis in the bone marrow.
  - Allogeneic stem cell transplant may be an option in fitter patients <60 yrs of age who have a HLA identical donor in the setting of multiply relapsed disease or failure to respond to >2 lines of treatment, provided they achieve a CR/PR.
  - Novel therapies for LPL, ideally if available within a clinical trial, should be considered in refractory disease. These include thalidomide, lenalidomide, alemtuzumab, everolimus, carfilzomib, pomalidomide, ibrutinib, idealalisb and ofatumumab.

- WM-associated amyloidosis
  - A brisk response to reduce the paraprotein and light chain load is important to curb amyloid deposition, especially in the heart and kidneys. The preferred option for initial therapy is therefore a bortezomib containing regimen such as bortezomib/dexamethasone/rituximab. An alternative in bendamustine in combination with dexamethasone and rituximab. Autologous transplantation as consolidation should be considered in eligible patients.

6.6.1. Disease-related complications specific to WM

- Hyperviscosity is found in less than 15% of patients at diagnosis but can be life-threatening. Patients with symptomatic hyperviscosity and/or neuropathy can be referred for plasmapheresis. Plasmapheresis should be instituted promptly:
  - in patients with signs/symptoms of hyperviscosity irrespective of plasma viscosity (PV)
  - in patients with PV >5.5mPa
  - in patients with high vascular risk .Systemic therapy should be started simultaneously or soon after plasmaperesis.

  Avoid transfusion in patients with hyperviscosity/high PP.
- IgM-associated peripheral neuropathy most commonly manifests as a distal symmetrical sensorimotor neuropathy. Testing of serum antibodies to MAG (myelin associated glycoprotein), GM1 (ganglioside M1) and sulfatide supports the diagnosis but their absence does not exclude it. Treatment in the form of steroids, plasma exchange or IVIg is indicated for progressive neuropathy interfering with function.
- Cryoglobulinemia – symptoms and signs of type I (Raynaud's phenomenon, acrocyanosis, necrosis, ulcers, purpura) result from impaired blood flow in small vessels due to cryoprecipitation. The mechanism in type II cryoglobulinemia is the precipitation of IgG-IgM immune complexes resulting in glomerulonephritis, proteinuria, arthralgia and neuropathy. Symptomatic cryoglobulinemia may require treatment with intensive plasma exchanges in conjunction with corticosteroids, cyclophosphamide or azathioprine. Patients with hepatitis C associated cryoglobulinemia should receive indicated anti-viral treatment. Patients should be given advice on keeping peripheries warm.
- Cold haemagglutinin disease – chronic autoimmune haemolysis can occur with cold exposure to due to cold agglutinin activity of the IgM paraprotein in some cases (<10%). RBC agglutination in the peripheral circulation can result in Raynaud's phenomenon, acrocyanosis and livedo reticularis. Supportive transfusions and keeping the body warm should be advised. Treatment of recurrent

episodes of non- responsive severe haemolysis included steroids, alkylating agents, purine analogues but not proven efficacious. The use of anti-CD20 antibody achieved response rates of 45–58% but not sustainable responses. The combination of anti-CD20 and fludarabine showed 76% response rate.

- Rare complications
  - Amyloidosis: fatigue, weight loss, macroglossia, organomegaly/cardiomegaly, peripheral and autonomic neuropathy are common manifestations.
- Autoimmune cytopenias – refer to the LCA guidelines on chronic lymphocytic leukaemia and B-prolymphocytic leukaemia.
- Rare complications
  - Bing-Neel syndrome: CNS involvement in WM is rare. Signs and symptoms are related to the sites of CNS infiltration. Treatment options are limited but chemotherapy with IDARAM may be considered.

7. Management of Myeloma Emergencies and Complications

7.1. Spinal cord compression pathway

See LCA Acute Oncology Clinical 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 (≥2.9 mmol/L) should be corrected using intravenous fluid and an intravenous bisphosphonate (e.g. zoledronic acid 4mg or pamidronate 90mg).
- Bisphosphonate therapy may need to be repeated after 3–5 days if hypercalcaemia is not controlled. Zoledronic acid is the most effective but requires dose adjustment if there is renal impairment.
- 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 >2.5L/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 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.
- 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

- 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 10^9/L, or <20 x 10^9/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 benefit, with bortezomib-associated symptoms:
  - amitriptyline, pregabalin or gabapentin
  - 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
  - capsaicin cream
  - quinine sulphate tablets (for muscle cramps)
  - magnesium 250mg BD for muscle cramps if magnesium levels are low.

8.5. 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 the treatment pathway for cord compression in the LCA (see section 7.1)
  - 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 amargin.

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 or not 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%) [42, 43]
- IV Zoledronic acid (4mg monthly over 15/30 minutes) is the bisphosphonate of choice. Dose reduction is recommended if creatinine clearance <60 ml/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 can 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 vertobroplasty or kyphosplasty may be appropriate for vertebral fracture/disease for symptom relief. Cases should be discussed with local radiologist or spinal surgeon.
- Where appropriate referral to the multidisciplinary team and allied health care 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 (eg DVT, PE or line thrombosis). The highest period of risk is during the first 4-6 months of therapy. A number of 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. For low risk patients should be prescribed aspirin daily. For higher risk patients low molecular weight heparin (LMWH) or treatment dose warfarin should be used.[3, 44]

8.9. Infections and antimicrobial prophylaxis

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 not recommended, although those on treatment may require specific antimicrobial prophylaxis. The routine use of antibiotics at diagnosis is the subject of an ongoing clinical trial (TEAMM).
- 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.
- 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. Hepatitis B prophylaxis should be considered if prior hepatitis B infection and should be discussed with 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 (IvIg): routine IvIg is not recommended. However, patients who suffer from recurrent bacterial infections (≥3 bacterial infections/year requiring treatment), who have hypogammaglobulinaemia and have failed a trial of prophylactic antibiotics may benefit from monthly infusions of IvIg (0.4g/kg). Annual review to assess the efficacy of regular IvIg is required. If the number of recurrent infections has decreased, IvIg should continue.

8.10. Diarrhoea

Therapy with lenalidomide has been associated with onset of diarrhea reported to be associated with bile acid malabsorption. This has been reported to respond to reduction in dietary fat content and/or the use of a bile acid sequestrant such as colesevelam or colestyramine (4g daily).[45]

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 (see Appendix 5: LCA Holistic Needs Assessment Tool).

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 possible consequences of cancer and its treatment, signs of recurrence and other important information. (see Appendix 6: NCSI Treatment Summary).
- 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. Rehabilitation and Survivorship for Myeloma and Related Disorders

- Myeloma patients can develop multiple disease-related complications. Patients should have access to supportive care throughout their cancer pathway.
- The myeloma clinical nurse specialist (CNS) will continue to play an important and central role in the ongoing management of the patient at all stages of the disease pathway.
- Survivorship is defined as the physical, psychological, emotional, spiritual and financial issues relating to cancer and its treatments and applies from diagnosis until end of life. It focuses on the health and life of a person with cancer beyond the diagnosis and treatment phases. Family members, friends and caregivers are also part of the survivorship experiences. Please refer to the LCA Survivorship Guidelines for more information.
- The consequences of cancer and its treatment may be acute, short-term, or occur many years following treatment completion. Clinicians and those living with and beyond their cancer diagnosis should be alert to the possibility that new symptom presentations may be a consequence of the cancer or its treatment.
- In order to support people to proactively manage their ongoing cancer-related needs, end of treatment consultations should be routinely offered. These should include a holistic needs assessment (HNA) (Appendix 5) to address the person's individual concerns and a treatment summary (Appendix 6), which provides the person and their GP with a summary of their treatment, anticipated consequences of that treatment (short and long term), when to seek further support (including signs of recurrence) and their planned follow-up. In addition, a health and wellbeing event should be offered to all people completing their treatment.
- Referral to the appropriate services, including rehabilitation, should be considered for patients who have long-term consequences of myeloma and its treatment. Other key healthcare professionals such as physiotherapists, dietitians, occupational therapists and counsellors/psychologists can deliver important aspects of holistic myeloma care. This is particularly important with the improving long-term outcomes and the complications and toxicities that myeloma and its treatment can cause with respect to morbidity (e.g. bone disease, peripheral neuropathy, fatigue and renal impairment).
- Rehabilitation needs should be considered throughout the patient's pathway, and use of the HNA may be helpful in identifying when referral to the relevant allied health professional is indicated.
- One in four people living with and beyond a cancer diagnosis will develop some degree of psychological morbidity, with one in 10 requiring referral to a specialist counsellor, psychologist, psychiatrist or other mental health support professional. Use of the HNA as a screening tool should prompt early management by the CNS/medical team or allied health professional, and referral to a specialist when indicated.
- Support should also continue to be provided for family carers, who can experience anxiety, depression and significant changes to their lives in providing ongoing support to the patient.
- A nutrition screening tool should be completed regularly for all patients to identify malnourished patients and those at risk of malnutrition, to monitor changes in nutritional status and to prompt referral to a dietitian if needed.

- A referral to a dietitian should be made in the following instances:
  - patients experiencing side effects of treatment that have a prolonged impact on nutritional status (e.g. mucositis, taste changes, gastrointestinal disturbances, nausea) should be referred to a dietitian
  - patients who require artificial nutrition support, including enteral and parenteral nutrition, should be referred to a dietitian
  - patients with prolonged neutropenia should be referred to a dietitian for advice regarding a neutropenic diet.
- People reporting ongoing consequences such as fatigue, anxiety, pain should be considered for non-pharmacological intervention, including but not limited to, TENS (transcutaneous electrical nerve stimulation), complementary therapy and psychological intervention such as mindfulness.
- The involvement of the palliative care team may be required for difficult or complex symptom control needs. Referral to specialist palliative care should be made using the LCA specialist palliative care referral form (see Appendix 7: LCA Specialist Palliative Care Referral Form).

12. LCA Key Worker and Myeloma Clinical Nurse Specialist

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 to 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, 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 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.

13. Clinical Trials and Biobanking

Entry of patients into clinical trials is an important aim of the LCA. 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.

The LCA 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.

The LCA 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 the LCA's research and all patients should be offered the opportunity to provide samples to the biobank.

14. 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. The LCA Palliative Care Group's 'Triggers for referral' document should be used to prompt timely referral for specialist palliative care (see Appendix 7: LCA Specialist Palliative Care Referral Form).

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 which are available in all the cancer centres and units affiliated to the LCA. The LCA referral form for referral to specialist palliative care can be found in Appendix 7: LCA Specialist Palliative Care Referral Form.

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.

15. 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 7). In line with peer review requirements, the LCA Haemato-Oncology Pathway Group and the LCA Clinical Board review this data on a regular basis to ensure all patients receive treatments intended to provide the best possible outcomes, consistent across all MDTs.

References

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Annex 1: JACIE-accredited Transplant Centres in the LCA

Imperial College Healthcare NHS Trust

Dr Eduardo Olavarria

Consultant Haematologist

BMT Programme Director

Haematology Department

ICHNT

Hammersmith Hospital

Du Cane Road

London, W12 0HS

Tel: 020 8383 3237

Fax: 020 8742 9335

Email: eduardo.olavarria@imperial.nhs.uk

The Royal Marsden NHS Foundation Trust

Dr Mike Potter via 020 8661 3670
katrina.sharpe@rmh.nhs.uk

Dr Chloe Anthias, contact details as above.

Dr Mark Ethell, via 020 8661 3794,
PA: janet.bromell@rmh.nhs.uk

Department of Haemato-Oncology
The Royal Marsden NHS Foundation Trust

RS11, 2nd Floor, Orchard House,

Downs Road, Sutton,

Surrey, SM2 5PT

Tel: 020 8661 3670

Fax: 020 8642 9634 (safe haven)

Alternative email: katrina.sharpe@nhs.net

St George's University Hospitals NHS Foundation Trust

Dr Mickey Koh

Director: Stem Cell Transplantation

Consultant Haematologist

St George's Hospital and Medical School

Jenner Wing Corridor 6

Blackshaw Road

London, SW17 0QT

Tel: 020 8725 3545

Fax: 020 8725 2859

Email: mickey.koh@stgeorges.nhs.uk

King's College Hospital NHS Foundation Trust

Bone Marrow Transplant Team

4th Floor, Hambleden Wing

King's College Hospital

Denmark Hill

London, SE5 9RS

Tel: 020 3299 4694, 020 3299 5268

Annex 2: Multidisciplinary Teams (MDTs) and Constituent Hospital Trusts

South East London MDT 1	Guy's & St Thomas' NHS Foundation Trust/Lewisham and Greenwich NHS Trust (Lewisham Hospital and Queen Elizabeth Hospital)
South East London MDT 2	King's College Hospital NHS Foundation Trust (including Princess Royal University Hospital)
South West London MDT 1	Kingston Hospital NHS Foundation Trust/St George's University Hospitals NHS Foundation Trust
South West London MDT 2	Epsom and St Helier University Hospitals NHS Trust/Croydon Health Services NHS Trust
South West London MDT 3	The Royal Marsden NHS Foundation Trust
North West London MDT 1	Imperial College Healthcare NHS Trust/The Hillingdon Hospitals NHS Foundation Trust/Chelsea and Westminster Hospital NHS Foundation Trust/West Middlesex University Hospital NHS Trust/Ealing Hospital
North West London MDT 2	The London North West Healthcare NHS Trust (Northwick Park Hospital and Central Middlesex Hospital)

Annex 3: 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 4: 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 (x 10^9/L)			
Platelet count (x 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 extramdeullary disease	Y / N		
Peripheral blood plasma cells	Y / N		

Annex 5: Waldenström's Macroglobulinemia

Summary of updated response criteria adopted at the 6th international workshop on Waldenström's macroglobulinemia.

Complete Response[3]	CR	lgM in normal range, and disappearance of monoclonal protein by inmunofixation; no histologic evidence of bone marrow involvement, and resolution of any adenopathy/organomegaly (if present at baseline), along with no signs or symptoms attributable to WM. Reconfirmation of the CR status is required by repeat immunofixation studies.
Very Good Partial Response	VGPR	A ≥90% reduction of serum lgM and decrease in adenopathy/organomegaly (if present at baseline) on physical examination or on CT scan. No new symptoms or signs of active disease.
Partial Response	PR	A ≥50% reduction of serum lgM and decrease in adenopathy/organomega (W present at baseline) on physical examination or on CT scan. No new symptoms or signs of active disease.
Minor Response	MR	A ≥25% but <50% reduction of serum IgM. No new symptoms or signs of active disease.
Stable Disease	so	A <25% reduction and <25% increase of serum lgM without progression of adenopathy/organomega, cytopenias, or clinically significant symptoms due to disease and/or signs of WM.
Progressive Disease[3]	PO	A ≥25% increase in serum IgM by protein confirmed by a second measurement or progression of clinically significant findings due to disease (ie, anemia, thrombocytopenia, leukopenia, bulky adenopathy/organomegaly) or symptoms (unexplained recurrent fever ≥38.4°C, drenching night sweats, ≥10% body weight loss, or hyperviscosity, neuropathy, symptomatic cryoglobulinemia, or amyloidosis) attributable to WM.

1 Treon SP, *et al.* Report from the Sixth lnternational Workshop on Waldenström's Macroglobulinemia. *Clin Lymph Myeloma Leukemia* 2011; **11**:69-73.

2 Varghese AM, *et al.* Assessment of bone marrow response In Waldenström macroglobulinemia. *Clin Lymph Myeloma* 2009: **9**:53-5.

3 Require two consecutive assessments made at any time before the institution of any new therapy.

Annex 6: Recommended Regimens for WM

CHOP-R

Cyclophosphamide	750mg/m^2 i.v., day 1
Doxorubicin	50mg/m^2 slow i.v. bolus, day 1
Vincristine	1.4mg/m^2 (max 2mg) i.v. bolus, day 1
Rituximab	375mg/m^2 i.v. infusion, day 1
Prednisolone	100mg po once daily, days 1-5

Repeat every 21 days up to 6 cycles

Chlorambucil +/- Prednisolone

Chlorambucil	8mg/m^2 po once daily, days 1-10
Prednisolone	40mg po once daily, days 1-10

Repeat every 4-6 weeks according to marrow tolerance

DRC

Dexamethasone	20mg iv on day 1
Rituximab	375mg/m^2 on day 1
Cyclophosphamide	100mg/m^2 bd orally on days 1-5

Repeat every 21 day cycle for 6 courses

Cladribine +/- R

Cladribine	0.12mg/kg sc on days 1-5
+/- Rituximab	375mg/m^2 weekly x 4

Repeated after 8 weeks (up to 2 courses)

Fludarabine

Fludarabine	40mg/m^2 p.o. once daily, days 1-5

OR

Fludarabine	25mg/m^2 i.v. once daily, days 1-5

Repeat every 28 days up to 6 cycles

BR

Bendamustine	90mg/m^2 days 1-2
Rituximab	375mg/m^2 day 1

Repeat every 28 days up to 6 cycles

BDR

Bortezomib	1.3mg/m^2 +
Dexamethasone	40mg days 1, 4, 8, and 11
Rituximab	375mg/m^2 day 11

OR

Bortezomib (1.6mg/m^2) +	
Dexamethasone	(20-40mg) on days 1, 8,15 and 22
Rituximab	(375mg/m^2 on day 8) for 4-8 cycles.

Repeat every 28 days up to 6 cycles

Campath

Alemtuzumab	30mg sc 3 x week for weeks 1-12

FCR

Fludarabine	40mg/m^2 p.o. once daily, days 1-3
Cyclophosphamide	250mg/m^2 p.o. once daily, days 1-3

OR

Fludarabine	25mg/m^2 i.v. bolus once daily, days 1-3
Cyclophosphamide	250mg/m^2 i.v. bolus once daily, days 1-3

Repeat every 28 days up to 6 cycles

Rituximab

Rituximab	375mg/m^2 weekly x 4

Salvage regimen for HSC Harvest:

R- DHAP

Rituximab	375mg/m^2 i.v., day 1
Dexamethasone	40mg orally, once daily, days 1-4
Cisplatin	100mg/m^2 i.v., infusion in 500mls-1litre 0.9% NaCl over 24 hours
Cytarabine	2000mg/m^2 12 hourly for 2 doses, i.v., infusion in 1 litre 0.9% NaCl over 3 hours (start time of each infusion is 12 hours apart)

Can repeat in 21-28 days as soon as blood recovery if required

R-ESHAP

Rituximab	375mg/m^2 i.v., day 1
Etoposide:	40mg/m^2 i.v. once daily in 250ml N/Saline over 1 hour, days 1-4
Methlyprednisolone:	500mg i.v. once daily in 100ml N/Saline over 30 mins, days 1-5
Cytarabine:	2000mg/m^2 i.v. single dose in 500ml N/Saline over 3 hours, day 1

Cyclo-G based on local centre policy dose of cyclophosphamide

IDARAM

Methotrexate	12.5mg intrathecal day 1
Idarubicin daily	10mg/m^2 i.v., days 1 and 2
Dexamethasone	100mg daily i.v. infusions of 12h duration, days 1-3
Cytarabine daily	1000mg/m^2 i.v. over 1 hour, days 1 and 2
Methotrexate	2000mg/m^2 i.v. over 2 hours, day 3

NOTE for all regimen follow local chemotherapeutic guidelines for dose adjustments based on renal, liver function, blood tests and for the supportive care for anti-emetics, stress-ulcer prophylaxis, hydration, anti-microbial, PCP, antiviral, antifungal prophylaxis.

Annex 7: Data Requirements

Haematology oncology services within the LCA 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

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 workings 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 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

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:
www.canceruk.net/rtservices/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

Local data requirements

The LCA Haematology Oncology Pathway group is working on developing a suite of metrics to inform the group and services within the LCA on areas of priority and potential service improvement. The LCA is currently collating information which is available through sources of data currently available, though the Haematology Oncology Pathway Group or LCA clinical board may require Trusts to submit additional MDT data to the LCA if additional priority areas are identified.

Annex 8: SIHMDS or Current Diagnostic Services and Contacts

Guy's & St Thomas' Hospitals NHS Foundation Trust

Cytogenetics/Flow Lab

ViaPath Pathology

4th Floor, Southwark Wing

Guy's Hospital

Great Maze Street

London, SE1 9RT

For APML diagnostic and MRD

Dr Yvonne Morgan

Molecular Oncology Diagnostics Unit

GSTT Pathology, 4th Floor, Southwark Wing

Guy's Hospital

Great Maze Street

London, SE1 9RT

Imperial College Healthcare NHS Trust

Imperial Molecular Pathology Laboratory

G Block, North Corridor

Hammersmith Hospital

Ducane Road

London, W12 0HS

King's College Hospital NHS Foundation Trust

KingsPath: Clinical Diagnostic Pathology Service

Haematological Medicine

King's College Hospital

Denmark Hill

London, SE5 9RS

London North West London Healthcare NHS Trust

Processed centrally in TDL laboratories on-site for SIHMDS (in progress), cytogenetics/molecular to:

North West Thames Regional Genetics Service, Haematology Section

Northwick Park Hospital

Watford Road

Harrow, HA1 3UJ

The Royal Marsden Hospital NHS Foundation Trust

The Centre for Molecular Pathology

Downs Road

Sutton, SM2 5PT

Tel: 020 8915 6570

Immunophenotyping Tel: 020 8915 6517 or 020 8915 6518

Cytogenetics Tel: 020 8722 4232

Molecular Genetics Tel: 020 8915 6565

Appendices

Appendix 1: 2 Week Wait Referral Forms

- North West London
- South East London
- South West London

Appendix 2: Treatment of Children

Appendix 3: Treatment of Teenagers and Young Adults

- Teenagers and Young Adults PTC Referrals
- Teenagers and Young Adults MDT Proforma

Appendix 4: LCA Key Worker Policy

Appendix 5: LCA Holistic Needs Assessment Tool

Appendix 6: NCSI Treatment Summary

Appendix 7: LCA Specialist Palliative Care Referral Form

Appendix 8: LCA Referral Criteria to Specialist Palliative Care

Published by London Cancer Alliance

London Cancer Alliance

5th Floor Alliance House

12 Caxton Street

London SW1H 0QS

www.londoncanceralliance.nhs.uk