Kent & Medway - Cancer

# The Management of Myeloma & Plasma Cell Disorders

## Oncological Treatment Guidelines for the Management of Multiple Myeloma and other Plasma Cell Disorders &

## Pathway of Care


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# 1.0 General Overview for Haematology

The purpose of these guidelines for patients diagnosed and treated for haematological cancer in Kent & Medway, is to describe the process for ensuring that all haematological cancer cases diagnosed within the Kent & Medway region are managed by the designated Haematological Cancer MDTs, achieving a coordinated seamless patient pathway in accordance with the best possible evidence based practice and to facilitate advancement in the specialty in the field of haematological cancer management.

**Notes:**

- The Kent & Medway - Cancer, Haematology Tumour Site Specific Group (TSSG) is responsible for agreeing all of the guidance
- The TSSG should consult with primary care members of the Kent & Medway Clinical Commissioning Groups (CCGs) regards the development of the pathway
- The purpose of the document is to provide a framework for the management of patients with suspected/confirmed haematological cancer
- The overall management details are largely reflected in the updated flow charts
- Information on MDT "functioning" is confined to the MDT Operational Policies based on the TSSG agreed "High Level Operational Policy" which is located on the Kent & Medway – Cancer website: http://www.kmcn.nhs.uk/home/resource-library

# 2.0 Scope

This Standard Operating Procedure (SOP) applies to all cases and suspected cases of Haematological Cancer within Kent & Medway and the haematological cancer specification of delivery of care requires all Trusts within Kent & Medway to adopt an agreed policy for the delivery of care. The policy relates to the expected pathway of care / treatment regimes for patients diagnosed with haematological cancer.

The policy covers the following:

- Access
- Initial Assessment
- Investigations
- Colorectal cancer multidisciplinary meeting (MDM)
- Surgical and non-surgical treatment
- Recurrent disease
- Follow up

# 3.0 Process and Terminology

## 3.1 Tumours

- B-Cell lymphoproliferative disorders including myeloma
- Chronic myeloproliferative disorders
- Acute lymphoblastic leukaemia
- Acute myeloid leukaemia
- Myelodysplastic syndromes
- Chronic myeloid leukaemia

## 3.2 Referral guidelines and process

- The incidental finding of haematological malignancy on specimens sent for routine examination is common. In these circumstances the haemato-oncologist will often be the clinician advising the GP that the patient requires an urgent appointment. Delays should NOT be built into the system by insisting on the use of a rapid access proforma.
- In the unlikely event that a GP receives a blood count/film reported as acute leukaemia (0r any of the conditions outlined above) and not directly contacted by a haematologist – the patient should be referred to a specialist immediately.
- Patients with spinal cord compression or renal failure suspected of being caused by myeloma require immediate referral to a haematologist.
- Patients with unexplained splenomegaly should be referred urgently to a haematologist.
- Patients referred to head & neck lump clinics who are found to have a haematological malignancy should be fast tracked to a haematologist. (The Head & Neck Pathway of Care reflects this course of action.)
- Patients with a “lump” referred to a surgeon and subsequently diagnosed with a haematological malignancy should be fast tracked to a haematologist.

## 3.3 GP alert (NICE: Referral guidelines for suspected cancer – June 2005)

- Combinations of the following signs and symptoms should alert GPs to perform a full examination, further investigations (including FBC and film) and possible referral:
    - Abdominal pain
    - Alcohol induced pain
    - Bleeding
    - Breathlessness
    - Bruising
    - Drenching night sweats
    - Fatigue
    - Fever
    - Lymphadenopathy
    - Recurrent infections
    - Splenomegaly
    - Weight loss

- GP investigations in patients with:
    - Persistent unexplained fatigue:
      Carry out an FBC, ESR & C-reactive protein. Repeat at least once if the patients condition remains unexplained and does not improve.

    - Unexplained lymphadenopathy:
      Carry out an FBC, ESR, & C-reactive protein.

- Any of the following additional features of lymphadenopathy:
    - Persistence for 6 weeks or more
    - Lymph nodes increasing in size
    - Lymph nodes greater than 2 cm in size
    - Widespread nature
    - Associated splenomegaly, night sweats or weight loss:
      Investigate further and/or refer.

    - Unexplained bruising, bleeding and purpura or symptoms suggesting anaemia:
      Carry out FBC, Film, Clotting screen, ESR, C-reactive protein.

    - Persistent and unexplained bone pain:
      Carry out FBC, X-ray, U&Es, LFTs, Bone profile, PSA (in males), ESR, C-reactive protein.

## 4.0 Imaging

Imaging guidelines for haematological cancer can be located on the Kent & Medway – Cancer website on the following link: http://www.kmcn.nhs.uk/home/resource-library/diagnostics-ccag/

## 5.0 Pathology

All Kent & Medway reporting pathologists follow The Royal College of Pathologists Histopathology Reporting on Cancers guidelines – a copy of which is available through the Kent & Medway – Cancer website:- http://www.kmcn.nhs.uk/home/resource-library/pathology-ccag/

http://www.rcpath.org/publications-media/publications/datasets/datasets-TP

## 6.0 Specialist Palliative Care and Support

All patients with a Haematological Cancer will have access to specialist palliative care and support at every stage of the patient journey.

Open and frank discussions with patients should take place with patients at all stages of their journey so that patients are not confused about their prognosis or have unrealistic expectations of any of the forms of treatment offered to them.

Relatives and carers will need to be appropriately supported and given appropriate information. However, in accord with the recommendations set out in various revised Improving Outcomes Guidance, relatives and carers should not be given information different to that given to the patient.

Frail and terminally ill patients with a Haematological Cancer should always be discussed with the specialist palliative care team.

Patients with end stage disease may choose to end their days at home and therefore the options should always be discussed openly with them and their relatives/carers.

Effective communication with primary care is essential.

All patients should have unlimited access to a Haematology Cancer nurse specialist who is a member of the specialist Haematology Cancer team

## 7.0 Follow Up

To be reviewed by Haematology TSSG during the period 2013/14.

## 8.0 Data

Collection of data at each stage of the pathway is the responsibility of the team looking after the patient at that time. The minimum dataset agreed by the TSSG will be a combination of those data items that meet national requirements, and additional items as agreed by the TSSG.

National data requirements will include:

- Cancer Waiting Times monitoring, including Going Further on Cancer Waits. The data items required will be as defined in ISB0147 at the time of referral and/or treatment.

  Details of the Cancer Waiting Times dataset are available from:
  http://nww.connectingforhealth.nhs.uk/nhais/cancerwaiting/documentation

  Cancer Waiting Times data will be submitted according to the timetable set out in the National Contract for Acute Services.

- The Cancer Outcomes and Services Dataset. The data items will be as defined in ISB1521, and any subsequent versions, at the time of diagnosis and/or treatment. The requirement will include those fields listed in the "Core" section of the dataset, and any additional tumour site specific sections, as applicable.

  Details of the COSD are available from:
  http://www.ncin.org.uk/collecting_and_using_data/data_collection/cosd.aspx

  Cancer Registration and Cancer Outcomes and Services (COSD) data will be submitted according to the timetable set out by Thames Cancer Registry.

- Where applicable, teams will also collect additional data items as defined in any corresponding National Clinical Audit Support Programme (NCASP) audit dataset.

  Details of these datasets are available from:
  http://www.ic.nhs.uk/services/national-clinical-audit-support-programme-ncasp/cancer

  Data for NCASP audits will be submitted, where applicable, according to timetables as agreed by the TSSG, and within the overall submission deadlines for each audit.

Submission of data to meet these national requirements will be the responsibility of each individual Trust.

Note that these standards are subject to variation from time to time, and where these requirements change, the data items required to be collected by the team will also change in line with national requirements.

Local data requirements will include any additional data items as agreed by the TSSG. These must be selected to avoid overlap with any existing data items, and where possible must use standard coding as defined in the NHS Data Dictionary.

Where possible and applicable, InfoFlex will be used for the collection and storage of data.

Additional areas of the COSD, relating to pathology, radiotherapy, SACT, diagnostic imaging and basic procedure details will feed into the dataset from other nationally mandated sources. It is the responsibility of each team to ensure that the whole of the relevant dataset is collected, and it is acknowledged that this may come from a variety of sources.

## 9.0 Personnel and Contact Information

A comprehensive, up to date list of MDM contact details can be found on the Kent & Medway – Cancer website via the following link: http://www.kmcn.nhs.uk/home/resource-library

# 10.0 Management of Myeloma

## 10.1 Introduction

The British Committee for Standards in Haematology (BCSH) in collaboration with the UK Myeloma Forum (UKMF) have issued comprehensive guidelines for the investigation, diagnosis, clinical management and supportive care of Multiple Myeloma[1;2]. Additionally guidelines are available for the management of Monoclonal Gammopathy of Uncertain Significance (MGUS)[3], Solitary Plasmacytoma of the Bone[4], Extramedullary Plasmacytoma[4] and AL Amyloidosis from the BCSH guidelines website (www.bcshguidelines.com).

The following guidelines describe the suggested initial investigation and clinical management of common plasma cell disorders (myeloma, MGUS, plasmacytoma and amyloidosis) as applicable to Kent & Medway - Cancer using level 1, grade A evidence where possible but should be used in conjunction with BCSH national guidelines.

All patients with a probable / possible diagnosis of a plasma cell disorder should be discussed with the local myeloma team (details in appendix 1) as soon as practicable particularly if urgent clinical intervention is necessary. All patients with a new diagnosis of a plasma cell disorder should be discussed in the Myeloma MDM (see appendix 1) to review investigations, confirm the diagnosis and plan clinical management. It is also suggested to discuss post treatment outcomes in the MDM to allow review of MDM decisions.

## 10.2 Investigation of suspected Plasma Cell Disorders

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

- Serum or urine monoclonal protein identified
- Abnormal serum free light chain ratio
- Presence of lytic lesions on radiological imaging
- Cast nephropathy / amyloid or light chain deposition on renal biopsy
- Unexplained immune paresis
- Circulating plasma cells on blood film
- Diagnosis of plasmacytoma on biopsy
- Unexplained hypercalcaemia
- Evidence of amyloid infiltration or light chain deposition
- Unexplained hyperviscosity syndrome

See Appendix 2 for frequency of myeloma presenting features. The following investigations represent the minimum required to ensure full diagnosis with prognostic information can be made.

### 10.2.1 History and examination

Full presenting history and examination

- In particular note bone pain, fatigue, recurrent infections, B symptoms, symptoms of hypercalcaemia or anaemia, neuropathy, GI disturbance, organomegaly, skin changes, medical co-morbidities, family history and occupational exposures

- Record ECOG performance status.

### 10.2.2 Peripheral blood tests

The following investigations should be carried out in all patients with a suspected plasma cell disorder:

- Full blood count (FBC), plasma viscosity (PV – if clinically indicated) and Erythrocyte Sedimentation Rate (ESR)
- Serum urea & electrolytes (U&Es) and liver function tests (LFTs)
- Serum albumin, corrected serum calcium and uric acid
- Serum protein electrophoresis and immunofixation
- Serum immunoglobulins and paraprotein quantitation
- Serum free light chains (sFLC) levels and ratio if available
- Beta-2 microglobulin
- C-reactive protein (CRP)
- lactate dehydrogenase (LDH)
- Serum vitamin B12 and folate
- Coagulation Screen

### 10.2.3 Urine Test

All patients should be screened for Urinary Bence Jones protein. Assessment of urinary protein is required if evidence of paraprotein or amyloid.

Urine electrophoresis (Bence Jones protein), including immunofixation
24 hour urine for creatinine clearance and urinary protein or urinary protein:creatinine ratio (as per local practice)

### 10.2.4 Bone marrow biopsy

Indicated for patients with significantly raised serum paraprotein (IgG >15 g/l, IgA > 10 g/l) any IgD or IgE, urine BJP > 500mg/l or sFLC (>500 mg/l), patients with paraprotein associated with anaemia, renal impairment, hypercalcaemia, immune paresis or lytic bone lesions and to complete staging investigations for patients with identified light chain or amyloid deposition

- Bone marrow aspirate & trephine
- Aspirate sample for cytogenetics / FISH and Aspirate sample for flow cytometry (mainly as part of clinical trial).

### 10.2.5 Imaging studies

Skeletal survey is required for all patients with a significant serum paraprotein or urinary Bence Jones protein or in patients with any level of paraprotein with bone pain.

- Skeletal survey: standard x-raysf the skeleton including lateral & AP cervical, thoracic and lumbar spine, skull, chest, pelvis, humeri and femora
- MRI scan for suspected spinal cord or nerve root compression or for assessment for severe bone pain in absence of lesions on plain x-rays
- MRI scan / CT scan following discussion with radiology to examine extent of soft tissue / bony lesions
- PET scan is not routinely indicated but may be of use to assess extensive soft tissue plasmacytomata (Do not perform within 3 months of radiotherapy or 4 weeks of chemotherapy)
- CT Chest/abdomen/pelvis as assessment of significant IgM paraprotein for lymphadenopathy

### 10.2.6 Other investigations

For confirmed amyloidosis

- Molecular characterization of amyloid subtype on tissue biopsy by DNA analysis / fibril sequencing at National Amyloid Centre (Royal Free Hospital, London)
- ECG, echocardiogram, NT-pro-BNP, troponin T (for amyloid staging)
- Renal / liver ultrasound
- SAP scan (at NAC, RFH, London)

For suspected POEMS syndrome

- Endocrine assessment
- US or CT abdomen to determine organomegaly

## 10.3 Diagnostic criteria

### 10.3.1 Diagnostic criteria for multiple myeloma

- 10% or more clonal plasma cells in bone marrow and / or a monoclonal serum protein of >30 g/l[5]
- Absence of lymphoproliferative disorder (e.g. lymphoplasmacytic lymphoma)

### 10.3.2 Diagnostic criteria for monoclonal gammopathy of uncertain significance (MGUS)

- Paraprotein <30 g/l and marrow plasma cells <10%[5]
- No evidence of myeloma related organ or tissue impairment
- No evidence of other B cell lymphoproliferative disorder

### 10.3.3 Diagnostic criteria for Solitary / multiple plasmacytoma of bone

- A single bone lytic lesion confirmed to be composed of plasma cells on biopsy[6]
- Absence of significant bone marrow plasma cell infiltrate (<10%)
- Presence or absence of monoclonal serum or urine protein
- Absence of evidence of plasma cell related organ or tissue injury other then bone lesion(s)

### 10.3.4 Diagnostic criteria for extramedullary plasmacytoma

- Soft tissue mass confirmed to be composed of plasma cells on biopsy [6]
- Absence of significant bone marrow plasma cell infiltrate (<10%)
- Presence or absence of monoclonal serum or urine protein
- Absence of evidence of plasma cell related organ or tissue injury

### 10.3.5 Diagnostic criteria for monoclonal deposition disease, including amlyoidosis

- 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)[6]
- Absence of significant bone marrow plasma cell infiltrate (<10%)
- Absence or presence of monoclonal serum or urine protein

### 10.3.6 Diagnostic criteria for POEMS syndrome

Mandatory Major Criteria[7]

- Presence of monoclonal plasma cell disorder (e.g. serum paraprotein)
- Peripheral neuropathy

At least one of the following:

  - Osteosclerotic bone lesions
  - Castlemans disease
  - Organomegaly
  - Endocrine disorder (excluding DM, hypothyroidism)
  - Skin changes
  - Oedema
  - Papilloedema

## 10.4 Staging and Risk Stratification

All newly diagnosed patients with a plasma cell disorder should be staged according to both the International Staging System[8] (ISS) and the Durie-Salmon Staging system[9] (EBMT requirement).
All patients with asymptomatic myeloma should be assigned to a risk category according to Mayo Clinic Criteria[10]. All patients with MGUS should be assigned to a risk category according to Mayo Clinic Criteria[11].

### 10.4.1 International Staging System (ISS) for Myeloma

The following criteria are used:[8]

- Stage I - Beta 2 microglobulin < 3.5 mg/l & Albumin > 35 g/l
- Stage II - Neither stage I nor stage III
- Stage III - Beta 2 microglobulin > 5.5 mg/l

| Stage | Criteria | Median survival in months |
|---|---|---|
| I | Serum ß2m < 3.5 mg/l & Serum albumin > 35 g/l | 62 |
| II | Neither I or III | 45 |
| III | Serum ß2m > 5.5 mg/l | 29 |

### 10.4.2 Durie-Salmon staging (DSS) for Myeloma

- Stage I - All of the following:[9]
  - Haemoglobin >10 g/dl
  - Serum calcium < 2.6 mmol/l
  - Normal skeletal survey or solitary bone plasmacytoma only
  - Paraprotein: IgG <50 g/l; IgA <30 g/l
  - Bence Jones protein <4 g/24h
- Stage II - Neither stage I nor stage III
- Stage III - One or more of the following
  - Haemoglobin <8.5 g/dl
  - Serum calcium >3.0 mmol/l
  - Advanced lytic bone lesions
  - PP: IgG >70 g/l; IgA >50 g/l
  - Bence Jones protein >12 g/24h
    - A: Relatively normal renal function (serum creatinine <200mmol/l)
    - B: Abnormal renal function (serum creatinine ≥200mmol/l)

### 10.4.3 Cytogenetics / FISH abnormalities

Cytogenetics / FISH is recommended at baseline to aid prognostication. The presence of t(4;14), t(14;16) and 17p- along with gains of 1q and loss of 1p as detected by FISH analysis have been observed to be poor prognostic indicators[1].

### 10.4.4 Differentiation between Asymptomatic and Symptomatic Myeloma

Symptomatic myeloma is defined by the presence of myeloma related organ or tissue injury (ROTI), commonly called the CRAB criteria. Myeloma with ROTIis classified as asymptomatic. ROTI includes the following:[1]

- **C**: Hypercalcaemia (Corrected Ca2+>0.25mmol/l above normal or >2.75 mmol/l)
- **R**: Renal impairment (no other cause)
- **A**: Anaemia (Hb <10 g/dl or <2 g below normal)
- **B**: Bone lesions (lytic lesions or osteoporosis with compression fractures)
- Symptomatic hyperviscosity
- Amyloidosis
- Recurrent bacterial infections (>2 in previous 12 months)

### 10.4.5 Asymptomatic Myeloma

The Mayo Clinic has devised a risk stratification approach for patients with asymptomatic myeloma that predicts likelihood of progression to symptomatic myeloma[10].

| **Risk Group** | | **Absolute risk of progression at 10y, %** | **Absolute risk of progression at 10y accounting for death as a competing risk, %** |
|---|---|---|---|
| **High Risk** | (Paraprotein ≥30g/l and BMPCs >10%)<br>FLC ratio: 0.125 – 8<br>FLC ratio; <0.125 or >8 | <br>58.8<br>83.8 | <br>51.3<br>75.2 |
| **Intermediate Risk** | (Paraprotein < 30g/l and BMPCs >10%)<br>FLC ratio: 0.125 – 8<br>FLC ratio: <0.125 or >8 | <br>58.3<br>68.5 | <br>40.4<br>56.8 |
| **Low Risk** | (Paraprotein ≥30g/l and BMPCs <10%)<br>FLC ratio: 0.125 – 8<br>FLC ratio: <0.125 or >8 | <br>32.2<br>33.3 | <br>22.8<br>25 |

### 10.4.6 MGUS

The Mayo Clinic have devised a risk stratification approach for MGUS to predict likelihood of progression to myeloma[11]. The following factors are markers of early progression and are additive: paraprotein ≥15g/l, non-IgG isotype, abnormal SFL ratio (<0.26 or >1.65 mg/l).

| **Risk Group** | **Absolute risk of progression at 20y, %** | **Absolute risk of progression at 20y 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 |

### 10.4.7 Plasmacytoma

The Mayo clinic have devised criteria to predict for progression of solitary bone plasmacytoma to myeloma based on sFLC and paraprotein level[12].

| Risk Group | Variables | 5 year progression rate |
|---|---|---|
| **Low** | Normal sFLC ratio<br>Paraprotein <5 g/ | 13% |
| **Intermediate** | Either variable abnormal | 26% |
| **High** | Abnormal sFLC ratio<br>Paraprotein ≥5g/l | 62% |

## 10.5 Disease monitoring and Assessment

Patients with symptomatic myeloma requiring therapy should have myeloma related parameters monitored at the beginning of each cycle of therapy using serum paraprotein or BJP (sFLC) as appropriate. In addition FBC, U&Es, bone profile, LFTs, glucose and CRP should be monitored at regular intervals appropriate to the type of therapy. Assessment of treatment response should be carried out at least every 2 cycles of therapy. Flow cytometric evaluation of MRD may be used in discussion with the myeloma team and flow lab and should be targeted for patients who have biochemical CR.

Patients with asymptomatic myeloma not requiring therapy should be monitored at regular intervals (every 2 – 4 months depending on clinical picture and Mayo risk category). FBC, U&Es, bone profile, CRP, paraprotein quantitation or BJP (sFLC) are required at each clinic visit. sFLC should be used to monitor light chain disease, AL Amyloidosis, non-secretory myeloma, IgD myeloma & plasmacytoma. Annual bone marrow aspiration/trephine and full skeletal survey (± CT/MRI/PET scan) are required for monitoring of non-secretory myeloma particularly if sFLC assay is normal.

### 10.5.1 Definitions of therapy

The number of lines of therapy should be recorded and defined together with depth of response and duration of response. A line of therapy is defined as one or more cycles of a planned treatment programme[13]. A new line of therapy is classified as occurring when

1. If <u>on-therapy</u> a planned course of treatment is modified due to progression or toxicity

2. If <u>off-therapy</u> a new course of treatment if required for progression / relapse.

*Examples:*
CTD x 6 is one line of therapy
CTD x 6 + Melphalan-200 autograft is one line of therapy if prospectively planned
CTD x 6 then Melphalan-200 autograft following relapse is two lines of therapy

### 10.5.2 Definition of response[13]

| | |
|---|---|
| **Complete Remission (CR)** | Negative immunofixation on serum and urine<br><br>Disappearance of any soft tissue plasmacytomas<br><br><5% plasma cells in bone marrow |
| **Stringent Complete Remission (sCR)** | As above and:<br><br>Normal serum free light chain ratio and no evidence of clonal PCs 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 BMPCs (if NSMM) |
| **Stable Disease / No response (SD)** | Not any of above and not progressive disease<br><br>Define the time to progression |

Response to both transplant and the line of therapy is required i.e. pre and post transplant comparison and pre and post line of therapy comparison. The term “plateau” is used to describe a sustained control of disease after maximum response to therapy and as such can apply to each response category.

### 10.5.3 Definition of relapse

| | |
|---|---|
| Progressive Disease (PD) | >25% increase in<br>Serum paraprotein (absolute increase >5g/l)<br>Urinary BJP (absolute increase >200mg/24h)<br>Difference between SFL (absolute increase >100mg/l)<br>Bone marrow PCs (absolute >10%)<br>New bone lesions / plasmacytomas<br>Myeloma related hypercalcaemia |
| Primary Refractory | Defined as having never achieved partial response on therapy (PR)<br>Non-responding, non-progressive<br>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 |

## 10.6 Indications for Treatment

Treatment is indicated for patients with symptoms or evidence of Myeloma-Related Organ or Tissue Impairment (ROTI) as described in section 4.4[1]

### 10.6.1 Definition of Progression from Asymptomatic to Symptomatic Myeloma

Any one of the following thought to be secondary to underlying plasma cell disorder

- Development of new soft tissue plasmacytoma or lytic bone lesions
- Hypercalcaemia
- Decrease in Hb by >2 g/dl
- Increase in creatinine to >180 ìmol/l

## 10.7 Chemotherapy for Myeloma

Despite advances in treatment, myeloma remains an incurable disorder. The aim of treatment is therefore disease control and prolonged survival whilst preserving a good quality of life. The use of autologous transplant for younger patients, improvements in supportive care for all and the introduction of novel therapies has meant year on year improvements in overall survival over the last 30 years[14].
However, with the absence of a cure and the continued refinement of induction and salvage approaches all patients should be considered for entry into clinical trials.

Network protocols giving full information on dosing, dose reductions, potential toxicity and suggested supportive medications are available for individual regimens and should be consulted prior to prescribing. Appendix 3 details a suggested treatment algorithm. All queries should be addressed to the Haematologic Oncology Pharmacist or Myeloma consultant.

### 10.7.1 First line chemotherapy

Melphalan has been at the core of myeloma therapy for five decades. Oral melphalan often in combination with steroids was the standard of care for myeloma treatment for many years for both young and elderly patients alike. The introduction of high dose melphalan with subsequent autologous stem cell support pioneered at the Royal Marsden Hospital rapidly became the treatment of choice for younger, fitter patients. This led to the concept of intensive and non-intensive treatment approaches for myeloma patients. The choice of first line therapy for myeloma therefore depends on the patients' suitability to undergo subsequent stem cell transplantation. All patients should be assessed for transplant suitability on the basis of performance status, co-morbidities and age. Fitter, younger patients should be treated with an intensive approach and older, less fit patients treated with a non-intensive approach. If there is doubt as to a patient's possible suitability for transplantation this should be discussed with the transplant team as early as possible in the treatment process. Preferably this decision will be taken within the context of the Myeloma MDM.

## 10.7.2 Patients suitable for Intensive Treatment

Myeloma therapy for younger, fitter patients follows two phases. Chemotherapy induction aims to achieve rapid cytoreduction and this is followed by consolidation using high dose melphalan and autologous stem cell rescue. An induction regimen that has anti-myeloma activity but is not stem cell toxic is used. Achievement of CR before or after autologous transplant is associated with superior progression free and overall survival compared with patients with poorer responses and the initial aim of therapy is therefore to administer adequate induction therapy to maximize early response and then enhance responses using high dose therapy. Several phase 3 studies have validated this approach including the UK MRC Myeloma VII study. In this study 86% of patients who received chemotherapy (CVAMP) and transplant (Melphalan-200) (v 48% for chemotherapy alone (ABCM)) achieved partial response or better after transplant with 44% (v 8%) gaining CR. This led to significant improvements in PFS (32 v 20 months) and OS (54 v 42 months)[15].

The current UK approach has centered on the recent Myeloma IX study which compared CTD with CVAD. Preliminary results show significantly improved responses for patients who received CTD both post induction therapy (>PR: 91 v 82%; CR: 21 v 14%) and post transplant (CR: 65 v 48%). Longer follow-up is required but projected median PFS is 27 months and OS is 5.5 years16. Several other phase 3 studies have examined combinations of novel therapies compared with conventional approaches which suggest improved response rates and progression free survival. The IFM group have compared bortezomib / dexamethasone with VAD and observed improved response rates (PR: 82 v 65%; >VGPR 39% v 16%) with improved PFS (69 v 60% at 2 years)17. The HOVON group compared bortezomib / adriamycin / dexamethasone (PAD) with VAD observing PR: 83% v 59% post induction rising to 93% v 80% post transplant (>VGPR 80% v 50%)18. An alternative approach combining bortezomib / thalidomide / dexamethasone (VTD) compared with TD has led to improvements in responses post induction (>PR: 94 v 79%; >VGPR: 62 v 29%) resulting in superior responses post transplant (tandem auto (>VGPR: 76 v 58%) and early improvements in PFS (90 v 80% at 2yr) and OS (96 v 91% at 2yr)19. Even more encouraging phase 2 studies incorporating lenalidomide / bortezomib / dexamethasone (RVD) with or without cyclophosphamide (CRVD) have reported early partial response rates of up to 100% with up to 75% of patients achieving VGPR pre-transplant20;21. However longer follow-up is required to determine if these novel combination approaches deliver markedly superior PFS and OS.
Current NICE guidance does not support the use of the novel therapies bortezomib or lenalidomide as initial myeloma treatment and outside of a clinical trial CTD has become the standard of care for patients for whom autologous transplant is planned. CVAD is a suitable alternative. Patients receiving induction therapy should be assessed after each cycle for disease response and patients with poor response after 2 cycles (progressive disease, no response) should be considered refractory and be considered to receive salvage therapy with a bortezomib containing regiment (e.g. Bortezomib / dexamethasone, PAD). Generally 4 – 6 cycles is required to attain maximum response.

## 10.7.3 Stem cell mobilisation

Early referral to the transplant team is advised (4th cycle) to allow for scheduling of stem cell mobilisation immediately following attainment of maximum response. A formal referral is required detailing presenting features, prognostic investigations (ISS and DSS), baseline disease status, treatment initiated and response to treatments. In addition full medical history and other notable features are required.

Several mobilisation regimens can be used. GCSF alone can be considered for patients who have demonstrated complete remission however a chemotherapy priming approach is generally used. The standard priming approach utilizes cyclophosphamide / GCSF. Younger patients who may undergo a second autograft and patients who may be difficult to mobilise due to previous chemotherapy can undergo a cytarabine / GCSF approach.

Patients receiving ESHAP, DHAP, DT-PACE or EDAP can be mobilized following these regimens. Patients who have failed prior mobilisation attempts or are predicted to be poor mobilisers (e.g. previous autograft) may be eligible to undergo mobilisation with the CXCR4 antagonist plerixafor (Mobilon). 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. For patients who may undergo two autografts the target should be 10 x $10^6$ CD34+ cells/Kg.

### 10.7.4 Patients not suitable for intensive treatment

The goal of non-intensive treatment for myeloma is the rapid and sustained control of disease with long progression free survival whilst maintaining quality of life. Treatment should be chosen according to co-morbidities and performance status.

Melphalan and prednisolone (MP) was the mainstay of non-intensive treatment for decades with partial response rates of around 50% and a plateau phase of 12 – 18 months before relapse. The introduction of thalidomide as a treatment for *de novo* myeloma has led to an improvement in responses and appears to be associated with improved PFS and OS in some combinations. A meta-analysis of six phase 3 studies comparing melphalan/thalidomide/prednisolone (MPT) with MP utilizing a range of intensities of melphalan, thalidomide or prednisolone dose with median ages at entry ranging from 69 to 79 years22 has reported. Response rates have been uniformly superior for patients who received MPT (≥VGPR: 25% v 9%; ≥PR: 34% v 28%). MPT associated PFS is reported to be superior to MP (20 months v 15 months) and this translates to an overall survival advantage in favour of MPT (39 months v 32.7 months)[22].

The addition of bortezomib to MP has also been studied in comparison to MP in the VISTA Phase 3 study[23]. Response rates were higher for those who received VMP compared with MP (≥PR: 71% v 35%; CR: 30% v 4%) and this translated into a significant improvement in duration of response (20m v 13m) and overall survival (87% v 78% at 16m) but at the cost of greater toxicity. Several ongoing studies for *de novo* myeloma are of potential interest for less fit patients.

The Myeloma IX study compared a dexamethasone attenuated CTD (CTDa) approach with MP with a significant improvement in response rates demonstrated (≥PR: 83 v 46%; ≥VGPR: 42 v 7%) and tolerable toxicity but without marked improvement in PFS 13 months (v 12.4 months) or OS 33 months (v 30.6 months)[24].

Several lenalidomide based induction regimens are under investigation. The ECOG group compared lenalidomide in combination with standard dexamethasone (RD) or attenuated dexamethasone (Rd) Superior responses were observed with RD (81% v 70% ≥PR) but at the cost of greater toxicity which led to a significantly superior PFS (25 months v 19 months) and OS (96% v 87% at 1 year) for those receiving Rd supporting the use of attenuated dexamethasone doses[25].

The use of MPT or VMP are recommended as initial treatment for newly diagnosed myeloma for patients who are not suitable for stem cell transplant. Regular monitoring (at start of each cycle) should take place to ensure adequate response is occurring. Consideration should be given to administering salvage therapy using an alternate approach for those with suboptimal response (<PR after 2 cycles) particularly if high risk disease (adverse cytogenetics) or renal impairment.

## 10.7.5 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. Early involvement of a 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. Following confirmation of diagnosis therapy should be initiated immediately. In a non-trial setting this can initially take the form of pulsed high dose dexamethasone (40mg od for 4 days). Standard frontline therapeutic regimens can be utilized but often require dose modifications as a result of the reduced glomerular filtration rate and with variable efficacy. 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 <10 ml/min.

Thalidomide, bortezomib and dexamethasone do not appear to 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 failure26. Lenalidomide requires dose adjustment depending on the degree of renal impairment according to manufacturers algorithm. 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.

It is suggested that all patients presenting with severe renal failure are managed in a centre with renal / myeloma expertise. For patients for whom stem cell collection is a consideration initial therapy is recommended with a bortezomib based approach (e.g. PAD) or CTD. Other patients should be treated with a bortezomib based treatment (e.g. CyBorDex or bortezomib / dexamethasone) or MPT. For patients for whom salvage of renal function remains a possibility regular sFLC should be monitored (weekly, pre-dialysis) and in the absence of improvement in renal function or significant reduction in light chain load consideration to using salvage therapy with a second line therapy e.g. a bortezomib based approach if thalidomide induction (PAD if transplant suitable) should be given.

High dose chemotherapy and stem cell transplant can be carried out in patients receiving regular dialysis and improvement / reversal of renal dysfunction may occur. However morbidity and mortality are significantly higher (TRM: minimum 20%) and as a result should be considered very carefully.

## 10.7.6 Plasma cell leukaemia

Plasma cell leukaemia may be primary (60%) or secondary (40%) to myeloma and is defined as the presence of >20% circulating plasma cells or an absolute level of 2 x $10^9$/L plasma cells. It is rapidly progressive and often associated with treatment refractoriness and early death. No consensus for treatment currently exists however in view of the aggressive nature of the disease rapid cytoreduction may improve outcomes. Several combination approaches have been described for aggressive (blastoid) / refractory variants of myeloma e.g. DT-PACE, ESHAP with the advantage that they can also be utilized for stem cell mobilization. Recent evidence has suggested that a bortezomib based approach may be of benefit (PAD). Early consolidation using autologous transplant should be carried out.

### 10.7.7 Primary refractory disease – Intensive approach

The aim for treatment of primary refractory disease continues to be cytoreduction prior to stem cell mobilization and subsequent autologous transplant. Combination chemotherapy regimens such as ESHAP have been associated with salvage of chemorefractory patients (responses in 67% of VAD refractory patients) with the advantage of stem cell mobilization following its administration however toxicity is high[27]. DHAP is an alternative platinum based salvage regimen. Bortezomib based combination approaches have also been employed for refractory patients and may be preferable due to rapid response with manageable toxicity (e.g. VelDex, PAD).

### 10.7.8 Primary refractory disease – non intensive approach

If stem cell transplant is not planned the patient should be reassessed to determine is myeloma continues to be symptomatic and therefore requires treatment. For those patients who have received a thalidomide based induction therapy a bortezomib based approach is likely to induce high response rates and is recommended (VMP, VelDex, CyBorDex) whereas patients who are refractory to primary bortezomib based therapy should receive a thalidomide based approach (MPT, CTD). For those patients with significant neuropathy precluding thalidomide or bortezomib therapy, lenalidomide / dexamethasone should be used.

### 10.7.9 Relapsed disease

All patients with myeloma will eventually relapse. Treatment should be within a clinical trial where possible. Suitability for subsequent high-dose therapy and stem cell rescue should be considered following re-treatment. Patients who are suitable for a second autograft should not be treated with a stem-cell toxic reinduction therapy. Second autograft alone is not advised if the duration of response was less than 12 months after initial transplant.

There is no uniformly established therapy for relapsed disease although several recent phase 3 studies have established bortezomib and lenalidomide as the standard for treatment of relapsed disease. The APEX study demonstrated superior efficacy for bortezomib over dexamethasone for relapsed disease[28]. 43% patients gained at least a PR (v 18% control) and this was associated with an improved duration of response (8m v 5.6m) and overall survival (30m v 24m). The addition of dexamethasone for suboptimal responses appears to further improve responses and recent studies on PAD, CyBorDex and VTD are associated with even better responses (>PR: 67 – 78%, 66%, 63% respectively) although long term follow-up and randomized comparison is required to prove superior efficacy[29-32]. Of particular note a study comparing PAD salvage therapy to initial VAD induction therapy (i.e. a “biological” control) observed improved responses with PAD for the majority of patients. The pivotal MM-009/-010 studies comparing lenalidomide / dexamethasone with dexamethasone alone have demonstrated the superiority of the lenalidomide based combination with pooled partial response rates of 61% v 23% that translated into a significantly improved PFS (11.2 v 5m) and OS (35m+ v 31m)[33-35]. As with bortezomib several combination regimens with lenalidomide have been reported such as RAD (lenalidomide / adriamycin / dexamethasone; >PR 69%, OS 88% at 1y) and CRD (≥PR: 62%)[36;37]. A recent phase 2 study examining RVD (lenalidomide / bortezomib / dexamethasone) has been found to be effective even in patients refractory to preceding bortezomib or lenalidomide (>PR: 67%)[38]. No randomized comparisons between bortezomib or lenalidomide based approaches have been carried out. Multiple other existing regimens incorporating conventional chemotherapy are available and may be of benefit if previous exposure to the class of agent has not occurred (e.g. intermediate dose melphalan, cyclophosphamide weekly).

With subsequent relapses repeat exposure to previously effective chemotherapy may produce further responses particularly if initial exposure was associated with a prolonged plateau. With multiple relapses additional factors such as performance status, medical co-morbidities, duration of response to prior therapies and residual treatment toxicities increasingly affect quality of life and it becomes increasingly important to take a multidisciplinary approach to symptom control and co-ordinated patient management with palliative care teams is likely to be of benefit.

Current NICE guidance recommends bortezomib can only be used as second line therapy whereas lenalidomide / dexamethasone are recommended for patients who have received at least two prior therapies. It is recommended to administer a bortezomib based approach as second line therapy and lenalidomide / dexamethasone as third line therapy.

Pomalidomide may be considered for patients who are PS 0-2 with relapsed and refractory disease who are refractory to bortezomib, lenalidomide and alkylating agents (failed treatment with bortezomib or lenolidamide is defined as progression on or before 60 days of treatment or progressive disease 6 or less months after achieving a partial response or intolerance to bortezomib).

## 10.8 Stem Cell Transplantation

### 10.8.1 Autologous Stem Cell Transplant

All medically fit patients should be considered for high-dose Melphalan (200mg/$m^2$) and autologous stem cell rescue as part of their 1$^{st}$ line therapy. This is associated with complete remission rates varying between 25-60%, a low TRM (<2%) and a median survival of approximately 5 years. Early discussion with the transplant team is suggested. Patients who relapse >12 months following 1$^{st}$ autograft and continue to be medically fit can be considered for second autologous transplant. Second autograft is not advised for those relapsing within 12 months of 1$^{st}$ autograft.

### 10.8.2 Allogeneic Stem Cell Transplant

Myeloablative allogeneic stem cell transplant can be considered in patients <40 years of age with an HLA-identical sibling. The treatment related mortality is high (up to 50%) but long term remission has been observed in up to 30% of patients. The use of Matched Volunteer Unrelated Donor full intensity transplants is not routinely recommended due to high procedural mortality.

Non-myeloablative or reduced intensity conditioning transplants (RIC) are currently experimental, and the best conditioning regimen is not yet known. They allow older patients to receive a sibling or unrelated donor transplant with less toxicity and acceptable TRM. Treatment using a RIC allogeneic approach should occur within a clinical trial.

### 10.8.3 Tandem Autologous Stem Cell Transplant

Trial evidence has suggested that tandem autografts may increase depth of remission after 1st high-dose chemotherapy but benefit is largely confined to those not achieving very good partial remission following 1st autograft and may not lead to overall survival gain. Tandem autografts are therefore not routinely recommended.

### 10.8.4 Stem Cell Transplantation in Severe Renal Failure

Autologous transplant may be considered for patients with severe renal impairment (creatinine clearance <30ml/min) but should only be carried out in a centre with special expertise and on-site dialysis unit. The TRM for patients with a creatinine clearance of 10-30ml/min and who are dialysis-independent is <4% whilst that in dialysis dependant renal failure (creatinine clearance <10ml/min) is reported in the order of 20%.

## 10.9 Supportive Treatment

Myeloma patients can develop multiple disease related complications. 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"[2]. Patients should be informed appropriately about their condition, its potential complications and the importance of supportive measures. They should be given written information e.g. Myeloma UK, MacMillan or LRF booklets, and if appropriate informed of patient support organisations as detailed in appendix 1. A toxicity assessment should be carried out prior to each cycle of chemotherapy.

### 10.9.1 Anaemia

Anaemia is a common problem either at diagnosis or later in the disease course. This is often multifactorial due to marrow infiltration, renal impairment, folate deficiency and chemotherapy induced marrow suppression. Anaemia often improves following disease control by chemotherapy. 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 (Hb <10 g/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 <1 g/dl. The target Hb should be <12 g/dl. If there is no response after 8 weeks erythropoietin should be stopped. It should be noted that NICE has not recommended treatment with erythropoietin for cancer related anaemia.

### 10.9.2 Renal function

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. If the patient has established renal failure, management should involve a renal physician.

### 10.9.3 Infection

Myeloma is associated with an increased risk of infection as a result of deficits in 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.

All patients should receive vaccination against influenza, Haemophilus Influenzae and Streptococcus pneumonia although responses may be suboptimal. Post-transplant vaccination is also advisable.

Intravenous Immunoglobulins: Routine IvIg is not recommended. However, patients who suffer from recurrent bacterial infections (≥ 3 bacterial infections/year requiring treatment) and who have hypogammaglobulinaemia may benefit from monthly infusions of IvIg (0.4g/kg). Annual review to assess efficacy of regular IvIg is recommended. If the number of recurrent infections has decreased IvIg should continue.

### 10.9.4 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. Pamidronate 90mg or Zoledronate 4mg). Bisphosphonate therapy may need to be repeated after 3 - 5 days if hypercalcaemia is not controlled. Corticosteroids may also aid control of hypercalcaemia.

### 10.9.5 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. Symptomatic patients should be treated urgently with plasma exchange; isovolaemic venesection may be used if plasma exchange facilities are not immediately available. If transfusion is essential exchange transfusion should be performed. Chemotherapy should be instituted promptly. Asymptomatic patients with minor rises (viscosity <6 mPa) are not an indication for intervention.

## 10.9.6 Pain management

Pain is one of the commonest symptoms experienced by myeloma patients and control is of paramount importance. It is recommended to manage pain with the support of 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, Oxycontin) and Fentanyl patches. NSAIDs should be avoided in all patients with renal impairment and used in other patients for short durations only (<5 days). Amitriptyline, Gabapentin or Pregabalin are useful for treating neuropathic pain.

Chemotherapy / radiotherapy: Bone disease is an indication for treatment of myeloma and response to therapy is associated with reducing progression of bone disease. Radiotherapy may be indicated for severe localized pain due to bone infiltration or nerve root compression (see radiotherapy section 9.10).

Vertebroplasty/Kyphoplasty: Focal vertebral damage causing persistent pain (e.g. wedge collapse) despite chemotherapy / radiotherapy may be amenable to vertebroplasty / kyphoplasty.

## 10.9.7 Bisphosphonates

All patients with symptomatic myeloma (i.e. requiring treatment) should receive long-term bisphosphonate therapy regardless of whether or not bone lesions are present. Sodium clodronate (Bonefos; 1600mg od), pamidronate (90mg monthly) and zoledronic acid (4mg monthly) are all associated with a reduction in skeletal related events. The Myeloma IX study has 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%)[39]. Zoledronic acid is therefore the bisphosphonate of choice. 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 manufacturers guidance.

IV zoledronic acid (4mg monthly over 15 minutes) - not recommended if creatinine clearance <30ml/min. Oral sodium clodronate (1600mg daily) - 50% dose reduction if creatinine clearance 10-30ml/min, not recommended if creatinine clearance <10ml/min. IV pamidronate (90mg monthly over 1.5 hours) – Reduce infusion rate to 90mg over 4 hours if creatinine clearance 30 – 60ml/min. Reduce dose to 30mg over 2 – 4 hours if creatinine clearance 10 – 30ml/min.

Oral calcium and vitamin D supplementation is recommended with zoledronic acid to prevent hypocalcaemia.

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 (PR or greater), stopping therapy can be considered after 2 years. At the time of disease relapse bisphosphonate therapy should be reinstituted.

### 10.9.8 Spinal cord compression

Spinal cord compression due to malignant infiltration or vertebral collapse requires urgent management and referral. This is best investigated by MRI to define the site and extent of tumour. If there is evidence of spinal cord compression the patient should be discussed and referred as a matter of urgency with the on-call Clinical Oncologist (<24 hours) for consideration of local radiotherapy. Dexamethasone should be commenced immediately (8mg bd). Discussion should also be undertaken with the on-call neurosurgical team for consideration of the appropriateness of surgical decompression.

### 10.9.9 Peripheral neuropathy

Several chemotherapeutic agents for myeloma can be associated with the development of peripheral neuropathy particularly bortezomib, thalidomide and vincristine. 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 extremities. Additionally symptoms such as tinnitus, visual disturbance, changes in bladder or bowel function, muscle weakness or cramps and decreased ability to sense temperature can all occur. Close monitoring of symptoms and appropriate modification of dosing is critical to prevent worsening of nerve damage (see individual treatment protocols for dose adjustments). Several supportive supplements have been anecdotally associated with reduction or prevention of neuropathic symptoms. [Vitamin B group (B12, B6), Folic acid, Vitamin E, Fish oil, Acetyl l-carnitine, Alpha lipoic acid, Topical cocoa butter, Capsacin cream].

### 10.9.10 Radiotherapy

For consideration of radiotherapy, patients should be discussed at the Myeloma MDM with the Clinical Oncology team.

Radiotherapy can be considered for the following:

Cord or cauda equina compression due to myelomatous deposit. This is an emergency. Patients should be started immediately on steroids and the on-call Clinical Oncologist should be contacted. An MRI scan of the whole spine should be performed to enable accurate localisation of all the disease to facilitate radiotherapy. Radiotherapy should be commenced within 24 hours. Very rarely radiotherapy can be omitted/delayed if the patient is asymptomatic or there has been a complete response to initial steroids where there may be a case for upfront chemotherapy. However, the case should still be discussed with the on call Clinical Oncologist.

Painful bony lesion(s) or extramedullary myelomatous deposit(s) not responding to systemic treatment.

Post surgical stabilisation of myelomatous skeletal lesion. Radiation should be commenced within 2 weeks if possible and should cover all the prosthesis/pin with a 1-2cm margin.

## 10.10 Solitary Plasmacytoma (Bone and extra-medullary)

Treatment of choice is localised radical radiotherapy. Once myeloma has been excluded and after discussion at the relevant MDT meeting the patient should be referred to Clinical Oncologist. Response following radiotherapy may be slow (up to 6 months).

Close follow up to monitor for development of myeloma is important.

## 10.11 References


1. Bird JM *et al.* Guidelines for the diagnosis and management of multiple myeloma 2011. *Br J Haematol.* 2011;154(1):32-75.
2. Snowden JA *et al.* Guidelines for supportive care in multiple myeloma 2011. *Br J Haematol.* 2011;154(1):76-103.

3. Bird J *et al.* UK Myeloma Forum (UKMF) and Nordic Myeloma Study Group (NMSG): guidelines for the investigation of newly detected M-proteins and the management of monoclonal gammopathy of undetermined significance (MGUS). *Br J Haematol.* 2009;147(1):22-42.

4. Soutar R *et al.* Guidelines on the diagnosis and management of solitary plasmacytoma of bone and solitary extramedullary plasmacytoma. *Clin Oncol (R.Coll.Radiol.)* 2004;16(6):405-413.

5. International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *Br J Haematol.* 2003;121(5):749-757.

6. Kyle RA *et al.* Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. *Leukemia* 2009;23(1):3-9.

7. Dispenzieri A. POEMS syndrome: 2011 update on diagnosis, risk-stratification, and management. *Am J Hematol.* 2011;86(7):591-601.

8. Greipp PR *et al.* International staging system for multiple myeloma. *J.Clin.Oncol.* 2005;23(15):3412-3420.

9. Durie BG *et al.* A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. *Cancer* 1975;36(3):842-854.

10. Dispenzieri A *et al.* Immunoglobulin free light chain ratio is an independent risk factor for progression of smoldering (asymptomatic) multiple myeloma. *Blood* 2008;111(2):785-789.

11. Rajkumar SV *et al.* Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. *Blood* 2005;106(3):812-817.

12. Dingli D *et al.* Immunoglobulin free light chains and solitary plasmacytoma of bone. *Blood* 2006;108(6):1979-1983.

13. Rajkumar SV *et al.* Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood* 2011;117(18):4691-4695.

14. Kumar SK *et al.* Improved survival in multiple myeloma and the impact of novel therapies. *Blood* 2008;111(5):2516-2520.

15. Child JA *et al.* High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med* 2003;348(19):1875-1883.

16. Morgan GJ *et al.* Maintenance Thalidomide May Improve Progression Free but Not Overall Survival; Results from the Myeloma IX Maintenance Randomisation. *ASH Annual Meeting Abstracts* 2008;112(11):656.

17. Lonial S *et al.* Emerging combination treatment strategies containing novel agents in newly diagnosed multiple myeloma. *Br J Haematol.* 2009

18. Sonneveld P *et al.* First Analysis of HOVON-65/GMMG-HD4 Randomized Phase III Trial Comparing Bortezomib, Adriamycine, Dexamethasone (PAD) Vs VAD as Induction Treatment Prior to High Dose Melphalan (HDM) in Patients with Newly Diagnosed Multiple Myeloma (MM). *ASH Annual Meeting Abstracts* 2008;112(11):653.

19. Cavo M *et al.* Superior Complete Response Rate and Progression-Free Survival after Autologous Transplantation with up-Front Velcade-Thalidomide- Dexamethasone Compared with Thalidomide-Dexamethasone in Newly Diagnosed Multiple Myeloma. *ASH Annual Meeting Abstracts* 2008;112(11):158.

20. Kumar S *et al.* Safety and Efficacy of Novel Combination Therapy with Bortezomib, Dexamethasone, Cyclophosphamide, and Lenalidomide in Newly Diagnosed Multiple Myeloma: Initial Results from the Phase I/II Multi-Center EVOLUTION Study. *ASH Annual Meeting Abstracts* 2008;112(11):93.

21. Richardson P *et al.* Lenalidomide, Bortezomib, and Dexamethasone in Patients with Newly Diagnosed Multiple Myeloma: Encouraging Efficacy in High Risk Groups with Updated Results of a Phase I/II Study. *ASH Annual Meeting Abstracts* 2008;112(11):92.

22. Fayers PM *et al.* Thalidomide for previously untreated elderly patients with multiple myeloma: meta-analysis of 1685 individual patient data from 6 randomized clinical trials. *Blood* 2011;118(5):1239-1247.

23. San Miguel JF *et al.* Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *N Engl J Med* 2008;359(9):906-917.

24. Morgan GJ *et al.* Cyclophosphamide, thalidomide, and dexamethasone (CTD) as initial therapy for patients with multiple myeloma unsuitable for autologous transplantation. *Blood* 2011;118(5):1231-1238.

25. Rajkumar SV *et al.* Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. *Lancet Oncol* 2010;11(1):29-37.

26. Dimopoulos MA *et al.* Renal impairment in patients with multiple myeloma: a consensus statement on behalf of the International Myeloma Working Group. *J Clin Oncol* 2010;28(33):4976-4984.

27. D'Sa S *et al.* Etoposide, methylprednisolone, cytarabine and cisplatin successfully cytoreduces resistant myeloma patients and mobilizes them for transplant without adverse effects. *Br J Haematol.* 2004;125(6):756-765.

28. Richardson PG *et al.* Extended follow-up of a phase 3 trial in relapsed multiple myeloma: final time-to-event results of the APEX trial. *Blood* 2007;110(10):3557-3560.

29. Jagannath S *et al.* Bortezomib in combination with dexamethasone for the treatment of patients with relapsed and/or refractory multiple myeloma with less than optimal response to bortezomib alone. *Haematologica* 2006;91(7):929-934.

30. Kropff M *et al.* Bortezomib in combination with intermediate-dose dexamethasone and continuous low-dose oral cyclophosphamide for relapsed multiple myeloma. *Br J Haematol.* 2007;138(3):330-337.

31. Palumbo A *et al.* Bortezomib, doxorubicin and dexamethasone in advanced multiple myeloma. *Ann.Oncol* 2008;19(6):1160-1165.

32. Pineda-Roman M *et al.* VTD combination therapy with bortezomib-thalidomide-dexamethasone is highly effective in advanced and refractory multiple myeloma. *Leukemia* 2008;22(7):1419-1427.

33. Dimopoulos M *et al.* Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med* 2007;357(21):2123-2132.

34. Weber DM *et al.* Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med* 2007;357(21):2133-2142.

35. Weber D *et al.* Prolonged Overall Survival with Lenalidomide Plus Dexamethasone Compared with Dexamethasone Alone in Patients with Relapsed or Refractory Multiple Myeloma. *ASH Annual Meeting Abstracts* 2007;110(11):412.

36. Knop S *et al.* Lenalidomide, adriamycin, and dexamethasone (RAD) in patients with relapsed and refractory multiple myeloma: a report from the German Myeloma Study Group DSMM (Deutsche Studiengruppe Multiples Myelom). *Blood* 2009;113(18):4137-4143.

37. Morgan GJ *et al.* Lenalidomide (Revlimid), in combination with cyclophosphamide and dexamethasone (RCD), is an effective and tolerated regimen for myeloma patients. *Br J Haematol.* 2007;137(3):268-269.

38. Richardson P *et al.* Lenalidomide, Bortezomib, and Dexamethasone in Patients with Relapsed or Relapsed/Refractory Multiple Myeloma (MM): Encouraging Response Rates and Tolerability with Correlation of Outcome and Adverse Cytogenetics in a Phase II Study. *ASH Annual Meeting Abstracts* 2008;112(11):1742.

39. Morgan GJ *et al.* First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial. *Lancet* 2010;376(9757):1989-1999.

40. Kyle RA *et al.* Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin.Proc.* 2003;78(1):21-33.

## 10.12 Appendix 1 – Contact details for myeloma teams including Clinical Trials

Suitability for entry into Kent & Medway - Cancer agreed clinical trials should be a standard component of the MDM discussion on each patient with a Haematological Cancer.

Refer to the local research team who will provide on request an orientation handbook, list of current trials and associated trial protocols and summaries.

**Contact numbers**

**MTW – Clinical Trials Office** 01622 225033

**Darent Valley Hospital – Clinical Trials Office** 01322 428100 ext 4810

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**Patient Information / Support Groups**
Myeloma UK Infoline 0800 980 3332, www.myeloma.org.uk.
Macmillian 0808 808 00 00. www.macmillan.org.uk

## 10.13 Appendix 2 – Common Presenting Features

**Adapted from Kyle *et al. Mayo Clinic Proc* 2003[40]**

| Presenting feature | Frequency | Note |
|---|---|---|
| Bone marrow plasma cells >10% | 96% | |
| Serum paraprotein | 92% | Biclonal in 2% |
| Raised ESR (>20mm/h) | 84% | |
| X-ray abnormality | 79% | |
| Urine monoclonal protein | 78% | |
| Raised viscosity | 76% | |
| Anaemia (<12g/dl) | 73% | |
| Lytic lesions | 67% | |
| Bone pain | 58% | < 6 months 73%; <12 months 91% |
| Rouleaux formation | 56% | |
| Raised INR | 37% | |
| Fatigue | 32% | < 6months 90%; <12 months 96% |
| Weight Loss | 24% | >9kg 50% |
| Leucopaenia (<4 x 10^9) | 20% | |
| Osteoporosis | 20% | |
| Raised Creatinine (>175 umol/l) | 19% | |
| Raised Calcium (>2.75 mmol/l) | 13% | |
| Raised CRP (>5) | 10% | |
| Macrocytosis | 9% | |
| Raised Alk phos (>300U/l) | 9% | |
| Leucocytosis (>10 x 10^9) | 8% | |
| Raised LDH | 7% | |
| Paraethesia | 5% | |
| Thrombocytopaenia (<100) | 5% | |
| Hepatomegaly | 4% | |
| PB plasma cells | 3% | |
| Non-secretory | 3% | |
| Thrombocytosis (>500) | 2% | |
| Splenomegaly | 1% | |
| Lymphadenopathy | 1% | |
| IgG isotype | 52% | |
| IgA isotype | 21% | |
| Light chain only | 16% | |

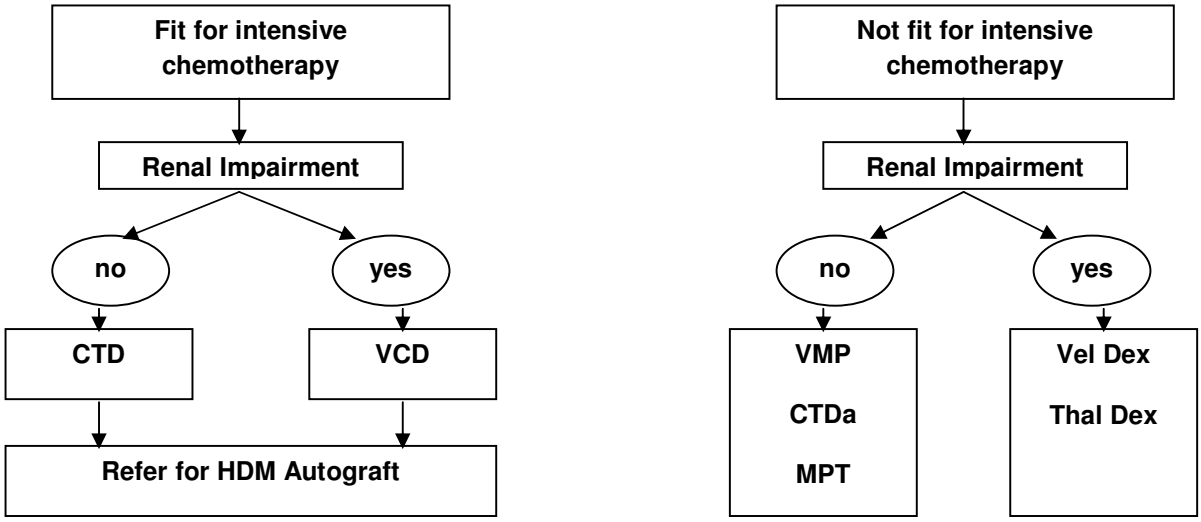
## 10.14 Appendix 3 – Suggested treatment algorithm

***CONSIDER ENTRY INTO A CLINICAL TRIAL WHERE APPROPRIATE***

***(for details on chemotherapy regimes refer to network chemotherapy prescribing manual at***

***http://www.kentmedwaycancernetwork.nhs.uk/resource-library/haematology-tssg/)***

***1st line therapy:***




***Relapsed and refractory disease***

Suggest use of doublet or triplet therapy containing anti-myeloma agents patient not previously exposed to e.g. if MPT first line therapy, consider VCD at first relapse.

- **Bortezomib**-based regimen e.g. **VCD**, **VMP**. 1st relapse *NICE TA 129.* 2nd relapse *funded via CDF*
- **Lenalidomide**-based regimen e.g. **RD, CRD**. 1st relapse *funded via CDF*. 2nd relapse *NICE TA 171*
- **Thalidomide**-based regimen e.g. **CTD**, **MPT**
- **Bendamustine**-based regimen *(CDF funded)*
- **Pomalidomide –**based regimen (CDF funded)
- **Intermediate-dose Melphalan**
- **ESHAP**

## 11.0 Glossary

Acronyms in common usage throughout Kent & Medway - Cancer documentation:

| | |
|---|---|
| CNB | Cancer Network Board |
| CYP | Children & Young People (in relation to the IOG) |
| DCCAG | Diagnostic Cross Cutting Advisory Group |
| TSSG | Tumour Site Specific Group (DOG/NSSG/TWG) |
| DVH | Darent Valley Hospital |
| EK | East Kent |
| EKHUFT | East Kent Hospitals University Foundation Trust |
| HoP | High Level Operational Policy |
| IOSC | Improving Outcomes: A Strategy for Cancer |
| K&C | Kent & Canterbury Hospital, Canterbury, (EKHUFT) |
| KMCN | Kent & Medway Cancer Network |
| KMCRN | Kent & Medway Cancer Research Network |
| LSESN | London & South East Sarcoma Network |
| MFT | Medway Foundation Trust |
| MTW | Maidstone & Tunbridge Wells NHS Trust |
| NOG | Non Surgical Oncology Group *(Permanent oncologist sub group of the TSSGs with a specific responsibility for chemo/rad pathways and advice to the TSSG, Network and geographical locations on new drugs)* |
| PoC | Pathway of Care *(Network agreed disease site specific clinical guidelines)* |
| QEQM | Queen Elizabeth the Queen Mother Hospital, Margate (EKHUFT) |
| QoL | Quality of life |
| RAT | Research and Trial Group *(Permanent sub-group of the TSSGs with a specific responsibility for taking forward the clinical trials agenda)* |
| RMH | Royal Marsden Hospital |
| RNOH | Royal National Orthopaedic Hospital |
| QVH | Queen Victoria Foundation Trust Hospital East Grinstead |
| UCLH | University College Hospital London |
| WHH | William Harvey Hospital, Ashford (EKHUFT) |
| WK | West Kent |
| CCG | Clinical Commissioning Groups |

# 12.0 Document Administration

| | |
|---|---|
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