Multiple Myeloma Guidelines

Approved by Pathway Board for Haematological Malignancies

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These guidelines should be read in conjunction with the latest National Cancer Drug Fund information, and all applicable national /international guidance.

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

Myeloma is a rare cancer with an annual frequency in the UK of around 50 cases per million, which seems to be increasing. The median presentation age is 70 years, with <2% presenting under 40 years. It is commoner in men and Afro-Caribbeans. Presenting features are varied and usually reflect end-organ dysfunction in the form of bone pain or pathological fractures, anaemia, increased infections, fatigue, renal failure or hypercalcaemia. Management hinges on prompt diagnosis and recognition of complications, many of which are fully reversible. As the condition is currently incurable, specific treatment is directed towards reducing disease burden in order to maximise the duration of periods of remission, reversal of end-organ damage, while minimizing acute and cumulative treatment-related toxicity.

These guidelines have been reviewed and updated following the original publication of the NLCN guidelines in 2009, by Percy et al. London Cancer guidelines published in July 2013 have been updated. There have been a number of large Phase 2 and 3 trials published which have changed standards of practice in the management of both newly diagnosed and relapsed patients. These guidelines reflect the views of the myeloma subgroup and where there is evidence this has been referenced in the document. For more extensive information, refer to the UK Myeloma Forum guidelines for the diagnosis and management of multiple myeloma (Bird J et al 2011), and guidelines for supportive care in multiple myeloma (Snowden J et al 2011)

The following is a schematic representation of the treatments available for patients. Please see text for detail.
2 Diagnosis & staging

2.1 Baseline investigations

Haematology
- FBC, clotting screen (PT, APTT, TT, fibrinogen)
- Group & save, direct antiglobulin test (DAT)
- HLA typing (consider for patients where an allogeneic transplant maybe considered)
- Bone marrow trephine & aspirate (with additional aspirate samples for cytogenetics/FISH)
  NB: cytogenetic/FISH information using CD138 selected cells is increasingly helpful in clinical decision-making and cytogenetics should include at least FISH for the following lesions: t(4;14), t(14;16), t(11;14), del(17p) and 1p-/1q+.

Biochemistry
- U&E, creatinine, urate, calcium, phosphate
- Liver function tests
- LDH
- Immunoglobulin levels, serum protein electrophoresis with immunofixation and paraprotein quantification
- Beta-2 microglobulin (β2M)
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- Creatinine clearance in any patient with renal impairment
- 24 hour urinary protein excretion with protein electrophoresis, immunofixation and quantification of Bence-Jones protein (BJP) (NB – spot urine for uBJP is not accurate for quantification, but maybe useful for monitoring)
- Serum Free Light Chain (SFLC) assay in all patients at presentation for prognostic purposes, and for monitoring those with a predominant light chain component

Virology
- Hepatitis B and C, +/- HIV if risk factors present

Radiology
- Skeletal survey (specify “for myeloma” – should include PA chest, AP & lateral cervical spine (including open mouth view), thoracic spine, lumbar spine, humeri & femora, AP & lateral skull and AP pelvis)
- MRI spine if
  i. neurological symptoms/signs of cord compression
  ii. patient presents with severe back pain not responding to simple analgesia or starting treatment with chemotherapy
  iii. the patient is asymptomatic with a normal skeletal survey. MRI may detect bone marrow infiltration and is useful in distinguishing benign from malignant osteoporotic fractures. Recent guidelines on the use of MRI have been published by the IMWG (http://www.ncbi.nlm.nih.gov/m/pubmed/25605835/). It should be noted that lytic lesions are best demonstrated by CT (either of focal area or low dose whole body CT).
  iv. for staging in all patients with apparently solitary plasmacytomas of bone (including MRI whole spine and pelvis). A CT-PET maybe an alternative imaging modality.
- Plain X-rays of any symptomatic areas not included within the survey, with additional CT imaging for clarification as needed, in accordance with BCSH Imaging Guidelines (D’Sa et al, 2007)

Cardiology
- ECG (+/-echo, MUGA as appropriate)

2.2 Diagnostic criteria

Treatment decisions in myeloma are guided by symptomatology and evidence of myeloma-related organ or tissue impairment (ROTI). The International Myeloma Working group drew up the following table (Table 1) to identify those patients with symptomatic myeloma who should start therapy.

<table>
<thead>
<tr>
<th>Table 1. Diagnostic criteria for MGUS &amp; myeloma</th>
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<tbody>
<tr>
<td>MGUS</td>
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<tr>
<td>M-protein in serum &lt;30 g/L</td>
</tr>
<tr>
<td>Bone marrow clonal plasma cells &lt;10% and low level of plasma cell infiltration in a trephine biopsy (if done)</td>
</tr>
<tr>
<td>No myeloma-related organ or tissue impairment (including bone lesions) or symptoms No evidence of other B-cell proliferative disorders or light-chain associated amyloidosis or other light-chain, heavy-chain or immunoglobulin-associated tissue damage*</td>
</tr>
</tbody>
</table>

* AL amyloid and the IgM paraprotein-related neurological syndromes would be instances of monoclonal gammopathy associated with specific syndromes
** Patients without symptoms but with significant myeloma-related organ damage are grouped with symptomatic myeloma because of the need for treatment
***No specific level required for diagnosis. A small percentage of patients have no detectable M-protein in serum or urine and a normal serum FLC ratio. However they have increased bone marrow plasma cells (ideally >10%) and apparent myeloma-related organ impairment (ROTI). This is termed non-secretory myeloma.

Adapted from International Myeloma Working Group, 2003
2.3 Myeloma related organ or tissue impairment (myeloma defining event)

This has been revised by the International Myeloma Working Group (Rajkumar et al 2014). Criteria for treatment could either be a myeloma defining event, ie evidence of organ damage that can be attributed to the underlying plasma cell proliferative disorder, or a biomarker of malignancy that would suggest a high chance of developing symptomatic disease (at least 80% requiring treatment within 2 years). We suggest clinicians exercise caution when using these biomarkers are used to initiate therapy.

<table>
<thead>
<tr>
<th>Table 2. Criteria for diagnosis of ‘symptomatic’ multiple myeloma</th>
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<tbody>
<tr>
<td>Hypercalcaemia</td>
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<tr>
<td>Renal insufficiency</td>
</tr>
<tr>
<td>Anaemia</td>
</tr>
<tr>
<td>Bone lesions</td>
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<tr>
<td>Other</td>
</tr>
<tr>
<td>Biomarkers of malignancy</td>
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</tbody>
</table>

*Where there is uncertainty as to whether or not organ or tissue impairment is attributable to myeloma the percentage bone marrow plasma cells should be >30%
Adapted from International Myeloma Working Group, 2014

2.4 Staging

The International Staging System (ISS; Table 3; Greipp et al, 2003) has now replaced the Durie-Salmon staging system. While it is valuable to determine stage at presentation, it does not appear to impact on prognosis to the same degree that it does in lymphoma or solid cancers.

<table>
<thead>
<tr>
<th>Table 3. International Staging System</th>
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<tr>
<td>Stage</td>
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<tr>
<td>I</td>
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<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
</tbody>
</table>

*2 subcategories:
• β2M <3.5mg/L but serum albumin < 35 g/L
• β2M 3.5 – 5.5 mg/L irrespective of serum albumin level
Adapted from Greipp et al, 2003

Combining ISS stage and cytogenetics is able to provide useful prognostic information. Based on large published series different groups have suggested various models. The International Myeloma Working Group suggests 3 risk stratifications as listed in Table 4 (Chng et al, 2014).

<table>
<thead>
<tr>
<th>Table 4. Risk Stratification</th>
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<tbody>
<tr>
<td>Risk</td>
</tr>
<tr>
<td>High risk</td>
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<tr>
<td>Standard risk</td>
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<tr>
<td>Low risk</td>
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</tbody>
</table>

Adapted from Chng et al, 2014
3 Management of Emergencies & Complications

3.1 Infections

The risk of infection is highest in the first 3 months after diagnosis and decreases with response to treatment (Perri et al, 1981; Lenhoff et al, 2000). Streptococcus pneumoniae, Haemophilus influenzae and Escherichia coli are the most frequent causes of infection in myeloma patients (Savage et al, 1982; Jacobson and Zolla-Pazner, 1986; Rayner et al, 1991).

Any febrile myeloma patient should be treated promptly with broad-spectrum antibiotics. Intravenous antibiotics are required for severe systemic infection or neutropenic sepsis. Aminoglycosides should be avoided, if possible. See section 5.2 for further guidance on managing infections.

There is currently a randomized study looking at the benefit of prophylaxis with a quinolone antibiotic in newly diagnosed patients requiring treatment (TEAMM trial).

3.2 Cord compression

The clinical features and management of impending/actual cord compression in the context of spinal disease depends upon the nature of the cord compression (due to bony/structural lesion or due to soft tissue disease), the spinal level, the extent of disease in the vertebral column and the status of disease elsewhere in the patient. It is a medical emergency and requires rapid diagnosis with treatment within 24 hours of presentation.

- Urgent MRI of the whole spine should be obtained and be available for discussion with neurosurgical and radiotherapy colleagues. Where MRI is unavailable or impossible due to patient intolerance or contraindication, an urgent CT scan should be performed.
- Start dexamethasone 40mg od orally for 4 days immediately.
- Refer to Mr Sean Molloy at RNOH, Stanmore (or other orthopaedic surgeon) for opinion on spinal stability, and whether patient would benefit from a brace
- Neurosurgery is usually undertaken for emergency decompression in the setting of structural compression (i.e. bony or tumour infiltration of vertebral canal) and/or to stabilize the spine.
- Surgery is usually consolidated by post-operative radiotherapy. When neurosurgery is not undertaken, patients should receive local radiotherapy and/or be commenced on definitive chemotherapy as soon as possible.
- The dose of radiotherapy and decisions regarding the institution of systemic treatment will depend upon the status of disease elsewhere.
- Advice regarding mobilisation of the patient should be sought from the neurosurgical team and the need for thromboprophylaxis must be considered.

3.3 Hyperviscosity

This is characterized by the presence of symptoms such as

- blurred vision
- headaches
- mucosal bleeding
- heart failure

Fundoscopy may demonstrate retinal vein distension, haemorrhages and papilloedema.

Patients usually have increased plasma viscosity. This is measured relative to water and is normally 1.4 to 1.8 mPa. Symptoms of hyperviscosity usually appear when it exceeds 4 or 5 mPa. This usually corresponds to a serum IgM level of at least 30 g/l, an IgA level of 40 g/l and an IgG level of 60 g/l (Mehta and Singhal, 2003). Unfortunately the plasma viscosity assay tends to have a long turnaround time, so is not generally used to guide acute clinical decision-making.
Management

- Urgent plasmapharesis with saline and albumin replacement.
- If plasmapharesis is not immediately available but hyperviscosity symptoms are present, consider isovolaemic venesection with N/saline IV infusion as a holding measure.
- Consider measuring PV before and after procedure – DO NOT WAIT FOR RESULTS BEFORE TREATING.
- Patients may need further exchanges over the next few days until appropriate treatment is instituted. This is determined by symptoms, and any requirement for blood transfusion.
- Start treatment as soon as possible with dexamethasone 40 mg orally once daily for 4 days. This should be followed with definitive anti-myeloma therapy.
- Patients who are symptomatically anaemic with very high immunoglobulins (i.e. as above for IgM, IgA and IgG) may need plasmapheresis prior to blood transfusion.

3.4 Hypercalcaemia

This requires prompt recognition and treatment to minimise renal damage.

Management

- All patients need bisphosphonate therapy: give pamidronate 90mg (dose adjust for renal failure) IV by infusion over 90mins. If calcium remains high after 72 hours consider repeating dose or using a more potent bisphosphonate such as zoledronic acid 4mg IV over 5mins. Remember to dose modify appropriately if renal impairment present.
- Mild hypercalcaemia (corrected calcium 2.6-2.9 mmol/l) requires oral rehydration.
- Moderate to severe hypercalcaemia (corrected calcium ≥2.9mmol/l) requires intravenous rehydration. Consider furosemide as needed to aid fluid balance and renal clearance of calcium.
- Refractory patients may require IV corticosteroids. Denosumab should be considered in those refractory to other treatments, or in whom bisphosphonates are contra-indicated due to renal dysfunction.

Patients may also have renal impairment/frank renal failure and they should be managed in conjunction with the renal team.

3.5 Renal failure

Renal failure is likely to be multifactorial, related to the light chain load and often potentiated by hypercalcaemia, dehydration, hyperuricaemia, infection and use of nephrotoxic drugs, including non-steroidal anti-inflammatory medication. More unusually there may be a contribution from amyloid, light chain deposition disease and plasma cell infiltration.

Management of acute renal failure

- Prevention by encouraging a high fluid intake (at least 3 litres/day) throughout the course of the disease, both on and off therapy. Avoid potentially nephrotoxic drugs such as NSAIDs and aminoglycosides.
- Rehydration, usually with IV fluids; some patients may require central venous pressure monitoring to guide fluid replacement.
- Hypercalcaemia should be treated with pamidronate as above (with appropriate dose modifications depending on renal function; see section 5.1 for full details on bisphosphonate use).
- Treat infection vigorously.
- Perform 24-hour urine collection to quantify protein (including albumin) excretion and Bence Jones protein excretion. This may help delineate the aetiology of acute renal failure where multiple causative factors are present.
- Start definitive treatment of myeloma with high dose steroids (dexamethasone 40mg po daily, or methyl prednisolone 1.5g IV daily for 4 days) should be done urgently as soon as the diagnosis of myeloma kidney is strongly suspected. Bortezomib combination induction regimes (bi-weekly bortezomib for the first cycle) are preferred in this setting. (see section 4.2.1).
- Start allopurinol at 100 mg daily.
All patients should be managed in conjunction with the renal team, especially if renal function does not improve within 48 hours of rehydration and correction of hypercalcaemia. Renal biopsy may help distinguish between patients with acute tubular necrosis whose renal function will usually improve with time, and those with amyloid and light chain deposition, whose renal function may only improve following successful treatment of the myeloma. Where appropriate, dialysis should be offered to patients.

**Chronic renal impairment**

All patients with chronic renal impairment (creatinine clearance<50ml/min) should be referred to the renal team for outpatient review.

- Analgesia requires special consideration, as NSAIDs must be avoided. Opiates should be used with caution given risk of accumulation. Consider radiotherapy for pain management early.
- Erythropoietin therapy may be valuable (see section 5.4).

### 3.6 Cryoglobulinaemia

Patients with myeloma may have Type I cryoglobulinaemia, where the paraprotein, or light chain, precipitates out at low temperature. Patients may present with swollen, painful, discoloured extremities; signs and symptoms may resemble those of Raynaud’s syndrome or a vasculitis. Mixed cryoglobulinaemia (Type II) is seen in association with a monoclonal IgM paraprotein with rheumatoid factor activity. It binds to polyclonal IgG, causing immune complex formation and is seldom seen in myeloma.

Patients should be advised to keep warm and may need plasmapheresis, in addition to definitive treatment for their plasma cell dyscrasia.
4 Chemotherapy

4.1 Introduction

4.1.1 Division of pts into young/fit for HDT & older/not fit for HDT

Patients with asymptomatic or “smoldering” myeloma do not require treatment with chemotherapy. They require observation and close monitoring for development of symptoms or changes in disease parameters (monoclonal protein concentration, renal function, development of marrow compromise or bone disease).

Symptomatic patients require treatment and should be assessed at the outset regarding their overall fitness for therapy, taking into consideration age and co-morbidities. Broadly, those ≤ 65 years (and in selected patients up to age 70 years) are considered fit for more aggressive systemic chemotherapy (“induction”), consolidated with high-dose melphalan (HDM) and autologous stem cell transplantation (ASCT) (also known as “high dose therapy”, HDT). The aim of induction and consolidation therapy in this group is to achieve maximum depth of response as this is felt to correlate with longer disease free survival and potentially better overall survival.

Those >65 years or with significant co-morbidities may not tolerate such a treatment approach, however HDT can be considered in selected patients depending on associated co-morbid conditions. Newer therapies such as bortezomib and lenalidomide are generally well-tolerated and achieving a deep and durable response may still be possible, even without consolidation with HDT. See section 4.5 for full details.

Elderly (>75 years) and more frail patients may get significant benefit from less intensive chemotherapy as reducing their disease burden should help control symptoms and reverse myeloma-ROT.I.

FOR ALL PATIENTS IT IS IMPORTANT TO CONSIDER CLINICAL TRIALS

All patients require good supportive care (section 5) but it is of particular importance in older patients.

FOR FULL DETAILS OF DOSING, DOSE MODIFICATIONS, SUPPORTIVE REGIMENS & NOTABLE TOXICITY PLEASE SEE APPENDICES (SECTION 6.2).

4.1.2 Assessment of response

After each cycle of chemotherapy, the following investigations should be performed:

- FBC
- Urea & electrolytes, creatinine, calcium,
- Liver function tests
- Serum immunoglobulins
- Monoclonal protein quantification:
  - For those with quantifiable serum paraprotein.
  - For those with light chain-only (Bence Jones) myeloma, monthly 24-hour urine collections are required to quantify uBJP, where informative (i.e. if elevated at diagnosis; Mead G et al, 2004), serial SFLC monitoring is a useful adjunct.
  - For those with oligosecretory or non-secretory myeloma, serial SFLC monitoring is useful.
- Those with truly non-secretory myeloma (i.e. normal serum and urine electrophoresis and normal absolute SFLC and ratios) require serial BM trephines -every 3 to 4 cycles of chemotherapy (approximately 3 months) unless there is clinical evidence of disease progression such as new bone pain or hypercalcaemia.

Formal re-staging to assess response to first line therapy should be undertaken after 4 cycles of chemotherapy unless there is clear evidence of disease progression through the first 3 cycles. Disease plateau should be taken as stable disease parameters, e.g. paraprotein, for at least 2 cycles. Response to therapy is graded by the International Response Criteria (appendix 6.1).

NB. Formal re-staging does not necessarily require a repeat BM aspirate & trephine.
4.2 Initial “induction” treatment for young, HDT candidates

Where possible patients should be offered treatment in a clinical trial.

If a patient does not wish to enroll in a clinical trial, the following treatments should be considered.

4.2.1 1st line:

Bortezomib regimens

The aim of induction treatment is to achieve the deepest possible response using a stem cell-sparing regimen prior to consolidation with high dose therapy (HDT) and autologous stem cell transplantation (ASCT). Recent phase 3 studies have established bortezomib containing triplet regimens as being superior to traditional VAD-type regimens. In the GIMEMA study, the VTD (velcade, thalidomide and dexamethasone) regimen produced an overall response rate (ORR) of 93% compared to 79% with Thalidomide and Dexamethasone, with corresponding ≥VGPR rates of 62% vs 28% (Cavo et al, Lancet 2010). The HOVON study reported an ORR of 78% to PAD (bortezomib, doxorubicin and dexamethasone) compared to 54% with VAD, and the ≥VGPR rate was 42% with PAD, vs 14% with VAD (Sonneveld et al, 2012). The IFM reported a superior ORR with bortezomib and dexamethasone (Vel/Dex), compared to VAD in the IFM 2005-01 phase 3 study, and more recently reported high response rates (≥VGPR 49%) with the attenuated vTD regimen (reduced dose bortezomib of 1mg/m²) in a phase 2 randomised study (Moreau et al, 2011). Response rates increased following ASCT in all studies, and progression-free survival was superior in patients receiving bortezomib in both the HOVON study and the GIMEMA study, while a favourable effect on OS was seen in the HOVON study (this may have been due to the use of fortnightly bortezomib maintenance). Finally, the addition of cyclophosphamide to bortezomib in the CyBorD regimen also produces deep response, with a ≥VGPR rate of 71% (Reeder et al, Leukemia 2009).

Due to the superior survival benefit, we recommend a bortezomib based induction regimen for this group of patients. Bortezomib is approved by NICE for its use in the upfront setting in combination with Dexamethasone either alone or in combination with Thalidomide. The following regimens are suggested: BCD-CYBORD, PAD or VTD.

Patients with >G2 neuropathy, or G2 neuropathy with pain should be treated on a less-neurotoxic regimen. Lenalidomide Dexamethasone (section 4.2.3) would the treatment of choice for this group of patients.

Bortezomib regimens

**BCD/CYBORD (BORTEZOMIB/ CYCLOPHOSPHAMIDE/ DEXAMETHASONE)**

Bortezomib 1.3mg/m² SC, D1, 8, 15 & 22
Cyclophosphamide 500mg po, weekly (e.g. D1, 8 & 15)
Dexamethasone 20mg po, day of bortezomib & day after (i.e. D1, 2, 8, 9, 15, 16, 22 & 23)
*Repeat every 28-35 days.*

**PAD (WEEKLY BORTEZOMIB)**

Bortezomib 1.3mg/m² SC D1, 8, 15 & 22
Doxorubicin 9mg/m²/day IV bolus injections D1, 2, 3, 4
Dexamethasone 40mg orally, D1-4 (with additional pulses D8-11 & D15-18 in cycle 1)
*Repeat every 28 days.*

**PAD for patients in renal failure or on dialysis**

Bortezomib 1.3mg/m² SC D1, 4, 8 & 11
Doxorubicin 18mg/m² by bolus injections D1
Dexamethasone 40mg orally, D1-4 (with additional pulses D8-11 & D15-18 in cycle 1)
*Repeat every 21 days.*

**VTD**
Bortezomib 1.3mg/m² SC, D1, 8, 15&22
Thalidomide 100-200mg orally daily
Dexamethasone 20mg po, day of bortezomib & day after (i.e. D1, 2, 8, 9, 15, 16, 22 & 23)
Repeat every 28 days.

REFER TO APPENDIX 6.2.3 FOR SUGGESTED DOSE MODIFICATIONS & SUPPORTIVE CARE.

### Important Bortezomib toxicities

- **Peripheral neuropathy, sensory & painful:** onset usually between cycles 3 and 4, but rare cases may have severe, sudden onset in cycle 1. Usually progressive once drug stopped. Often worsens during week off, perhaps related to lack of steroids during this week. Managed by early detection, prompt dose-reductions and good analgesia.
- **Gastrointestinal toxicity:** constipation (more common), diarrhoea, abdominal bloating or pain. Warn patients and have a low threshold for pre-emptive laxative use, or admission for hydration in those with severe diarrhoea, unresponsive to loperamide. These patients are at risk of developing pre-renal acute renal failure. Diarrhoea is less common and persistent or severe diarrhoea should raise suspicion of amyloid involvement.
- **Postural hypotension and pre-syncpe secondary to autonomic neuropathy:** With the use of SC drug, pre-hydration is no longer routinely used, so patients must be educated about oral hydration. Consider screening for pre-syncpe and syncope by measuring lying and standing BPs at start of each treatment cycle. Record use of anti-hypertensives, or alpha-blockers for benign prostatic hypertrophy (tamsulosin, alfuzosin), as these may need dose adjusting or stopping, in case of postural drop, and/or symptoms of postural dizziness or lightheadness. Many patients require dose adjustment of their usual anti-hypertensives for the duration of bortezomib therapy. Patients who have not had adequate oral hydration, or who have a postural drop of >10mmHg should have pre-hydration with IV saline infusion (250-500 ml) prior to treatment.
- **Thrombocytopenia:** usually progressive over 21-day bi-weekly cycle with recovery prior to next cycle, but less of a problem with weekly dosing. Check FBC on D1 & D8; consider dose reduction if platelets <30 on D1 and transfuse platelets if <30 on any other treatment day.
- **Fatigue:** this is often related to a lowering of BP, and is often a subtle manifestation of autonomic neuropathy

### Thalidomide regimen

For a small number of selected patients, an oral regimen may be preferable, eg in case of needle phobia. The CTD regimen produced superior response rates compared with C-VAD in the Myeloma IX study, but no benefit in terms of PFS or OS. However, for standard or intermediate risk patients who require an oral alternative, CTD (Cyclophosphamide, Thalidomide and Dexamethasone) should be considered. An alternative is Melphalan Prednisolone and Thalidomide (see section 4.4.2).

Details of regimens and attendant toxicities are given below.

**CTD (CYCLOPHOSPHAMIDE/ DEXAMETHASONE/ THALIDOMIDE)**
Cyclophosphamide 500mg po once weekly (D1, 8, 15 & 22)
Thalidomide (200 mg po as tolerated) once daily continuously (D1-28)
Dexamethasone 40mg po once daily D1-4, and 15-18*
Repeat each cycle every 28 days
*From cycle 4 reduce dexamethasone to D1-4 only.
REFER TO APPENDIX 6.2.1 FOR SUGGESTED DOSE MODIFICATIONS & SUPPORTIVE CARE. FOR SPECIFIC INFORMATION REGARDING THALIDOMIDE, SEE APPENDIX 6.2.2.
The RVD regimen is given below.

 Patients with high risk disease (see section 2.4) may benefit from the substitution of lenalidomide for thalidomide. Cytoreduction should receive dexamethasone 40mg weekly ("low dex") for the first 2 cycles. Patients on dialysis should start to receive their bortezomib injections bi-weekly (at least 72 hours between doses), on non-dialysis days or after completion of dialysis on the same day as dialysis. The intensity of bortezomib can be electively reduced to weekly once renal function has normalized and the light chain load reduced.

4.2.2 2nd line: Bortezomib-containing regimens

Patients who fail to respond (at least PR) to a non-Bortezomib regimen should receive salvage with Bortezomib, using one of the regimens above.

4.2.3 Salvage with IMiDs

4.2.3.1 Lenalidomide-containing regimens

Patients who are refractory to BCD/CyBORD may respond to substituting thalidomide for cyclophosphamide, i.e. change regimen to VTD. Patients refractory to VTD are more difficult, and should be managed on a patient-by-patient basis. One option would be to salvage with Lenalidomide (Revlimid) therapy. Lenalidomide is funded from the National Cancer Drugs Fund as second line for patients who received bortezomib at first line.

Lenalidomide should be prescribed with dexamethasone alone, or in conjunction with cyclophosphamide. Dexamethasone should be given as 40mg weekly ("low-dose dex") (Rajkumar et al, 2009). Patient requiring rapid cytoreduction should receive pulsed dexamethasone ("high-dose dex") for the first 1-2 cycles.

Patients with high risk disease (see section 2.4) may benefit from the substitution of lenalidomide for thalidomide. The RVD regimen is given below.

**LENALIDOMIDE/DEXAMETHASONE**

Lenalidomide 25 mg po, D1-21
Dexamethasone 20-40*mg po weekly, D1, 8, 15 and 22 ("low-dose")
+/-Cyclophosphamide 500 mg po weekly (e.g. D1, 8, 15)
Patients with stable, non-progressive disease may still benefit from HDT, but a more cytoreductive priming regimen, e.g. ESHAP, could be considered.

Patients should be referred to the myeloma team in a centre performing autologous stem cell transplantation for assessment and HDT work-up, ideally after cycle 4, even if maximal response has not been reached. This is to allow better planning for priming and stem cell harvesting dates. Once maximal response has been reached, or once patients have completed 6 cycles of chemotherapy (whichever comes first), patients should undergo priming and harvesting of stem cells. The priming chemotherapy should be timed to be at least 4-6 weeks from the end of the last cycle of induction to enable optimal bone marrow recovery and successful harvesting.

Patients in PR do not need to have a repeat BM trephine as part of their re-staging prior to referral and priming; most decisions regarding timing of harvest and time of mobilization protocol can be made using biochemical disease parameters (i.e. serum paraprotein, urine Bence Jones protein, SFLC). Consider a BM pre-HDT as a baseline.

Patients with stable, non-responsive, non-progressive disease should have a BM trephine to aid decision-making regarding the appropriateness of attempted harvest and the best priming regimen.
There is no cut-off level of bone marrow plasmacytosis for patients proceeding onto stem cell harvest, as there is no evidence that minimizing disease contamination of the graft has a real influence on outcome (Vescio et al, 1999). Similarly, published data do not show an advantage for patients receiving CD34+ selected grafts (Bourhis et al, 2007). Patients should have virology checked (HIV, HCV, HBV) as per local protocols.

Following stem cell collection, patients may proceed to a further 1 - 2 cycles of chemotherapy if plateau has not been reached, or there is an unavoidable delay before proceeding to transplant.

### 4.2.6 Cyclophosphamide & GCSF

This is the first-line priming approach and may be administered as an outpatient. Local guidelines should be followed. Leucaphareseis may need to be repeated over several days to obtain a minimum of 2-4x 10^6 CD34+ cells/kg. If the CD34+ cell yield after the first day of attempted harvest is low, Plerixafor (CXCR4-R antagonist) is given by SC injection 10 hours prior to further harvesting, in addition to further GCSF.

Alternatively, if patients fail to mobilise after cyclophosphamide priming with the use of Plerixifor, consider ESHAP priming.

### 4.2.7 ESHAP & GCSF

ESHAP and GCSF priming should be considered in those

- Who fail to mobilise after cyclophosphamide and GCSF
- With stable, non-responsive, non-progressive disease
- With heavy marrow plasmacytosis (i.e. >50%) – NB. Consider further cytoreduction with either up to 2 cycles of ESHAP (only in those with good renal function) or with a bortezomib-containing regimen (see section 4.2.2), as harvesting may be less successful in this group.

ESHAP is potentially nephrotoxic and therefore caution is required in those with renal impairment (at presentation or ongoing) or with light chain myeloma; such patients require a measured creatinine clearance before proceeding onto a course of ESHAP chemotherapy. All patients proceeding with this regimen need plentiful oral or intravenous fluids and careful fluid balance monitoring (see appendix 6.2.9).

- Etoposide 40mg/m² IV once daily, D1-4
- Methylprednisolone 500mg IV once daily, D1-5
- Cytarabine 2000mg/m² IV D1
- Cisplatin 25mg/m² daily by continuous IV infusion, D1-4 (total dose 100mg/m² over 4 days)
- GCSF on D6, repeated daily and monitor WBC
- REFER TO APPENDIX 6.2.9 FOR COMPLETE ESHAP PROTOCOL & SUPPORTIVE CARE.

Re-stage disease after ESHAP, and proceed to HDT unless there is progressive disease. If there is disease progression, consider 2nd or 3rd line induction chemotherapy (section 4.2.2 and 4.2.3). It may be necessary to re-consider the appropriateness of HDT in these patients.

### 4.3 High Dose Therapy

Patients under 65 years old with good performance status (and in selected patients up to 70 years old) should be considered for consolidation of their induction treatment with high dose therapy (HDT) and autologous stem cell transplantation (ASCT). An allogeneic transplant is not currently offered in place of an autologous transplant, but may be considered as a tandem reduced intensity procedure following recovery from autologous transplantation. It is reserved for those patients who are young and fit enough, and have high risk disease, on a case-by-case basis. For simplicity, it is recommended that any patient being considered for HDT with ASCT should be referred to the myeloma team and those in whom a tandem reduced intensity transplant is an option (younger, high risk patients, and those who have achieved at least a VGPR) will be discussed with the transplant team.
4.3.1 High Dose Melphalan and ASCT

Prospective randomized trials have now established a place for high dose therapy (HDT), which is superior to standard chemotherapy both in terms of event free survival and overall survival (Attal, et al 1996, Child, et al 2003). Patients above the age of 65 yrs should be carefully assessed (including echo/ MUGA scans, lung function tests, etc.) and counselled regarding the slightly higher risk in this age group. As discussed in section 4.1.1, the value of HDT in this group is less clear, even if they are apparently fit to receive it.

Criteria for proceeding to high dose melphalan and ASCT
- Patients achieving at least SD following induction therapy.
- Performance status ≤ECOG 2/ Karnofsky 70%.
- No significant cardiac disease. If in doubt, MUGA scan/echocardiogram and a cardiology opinion should be sought.
- Adequate harvest. The minimum CD34+ cell dose for unselected harvests is 2 x 10^6/kg. A dose of 1-2 x 10^6/kg may be acceptable, provided colony cultures yield a CFU-GM dose of 20 x 10^6/kg, depending on local policy.
- Age up to 70 yrs if good performance status with no other medical problems.

Consider Melphalan 140mg/m^2 in patients older than 65 years old, with co-morbidities, and in those with renal impairment (GFR <50 ml/min).

HIGH DOSE MELPHALAN (M200) AND AUTOLOGOUS STEM CELL TRANSPLANT
Melphalan 200mg/m^2* IV infusion, D -2**
Stem cells re-infused D 0
*The dose may be reduced to 140mg/m^2 see note above.
**May be given on D-1 if creatinine clearance >60ml/min. AS PER LOCAL POLICY.

Patients with severe renal failure
Those with chronic renal failure on dialysis or with creatinine clearance <40 ml/min should be treated in a centre that is able to provide renal support if needed. Stem cells can be collected and initially stored at centre even if they are unable to perform high dose therapy with renal support. These patients should receive melphalan 24 hrs before dialysis, with stem cells re-infused post dialysis. The dose of melphalan could be reduced to between 100 - 140 mg/m^2 at the discretion of the attending team.

4.3.2 Allogeneic transplant

Where possible patients should be enrolled in clinical studies assessing the benefit of allogeneic transplantation. Outside of clinical studies younger patients with high risk features, and who have achieved at least a VGPR to their ASCT, may benefit from a reduced intensity allogeneic transplant.

4.3.3 Consolidation/ Maintenance treatment following HDT

The aim of consolidation and maintenance is to improve the depth of response and extend the time until more treatment is required (ie to prolong PFS). Several phase 3 studies have been published recently, demonstrating clinical benefit, however no strategy has been adopted as the standard of care in this setting.

Thalidomide maintenance following HDT

Thalidomide maintenance following HDT improves PFS in 7 randomised trials and OS in 2 of these studies. This benefit is most marked in those patients who fail to achieve a VGPR, suggesting further cytoreduction is important. In those patients with del(17p) there appears to be a survival disadvantage to using thalidomide maintenance. This may relate to selecting out of drug resistant clones in this sub-group which renders the disease more chemoresistant (Morgan et al, 2012). Furthermore extended thalidomide treatment is limited by toxicity, namely peripheral neuropathy, with a median duration of around 12 months. Long term thalidomide maintenance is therefore not practical in the majority of patients.
The recommendation is that patients achieving a VGPR or CR following ASCT do not require maintenance. Patients achieving less than a VGPR following ASCT may benefit from maintenance therapy with single agent thalidomide to a maximal dose of 100mg. This should start 3 months following ASCT and continue for up to 1 year, stopped earlier if CR achieved. Ideally patients should be screened for del(17p) prior to starting, as thalidomide maintenance may worsen long term outcomes in this group.

**Lenalidomide maintenance following HDT**

Lenalidomide maintenance improves PFS following initial cytoreduction in three phase 3 studies (Attal et al, 2012, McCarty et al 2012, Palumbo et al 2012). In one study lenalidomide maintenance improved OS (McCarty et al, 2012). Lenalidomide is well tolerated, but may be associated with an increased risk of second primary malignancy, as reported in all 3 studies, although the risk maybe small compared to the potential benefit. As a result the duration of treatment has been limited to 2 years by the IFM group. Myeloma XI is currently assessing the role of Lenalidomide maintenance. Longer follow up of these trials to evaluate the response to salvage following relapse in the Lenalidomide maintenance arm is required before the true clinical benefit of this approach will be apparent.

The recommendation is that patients should only receive Lenalidomide maintenance in the context of a clinical trial, until more information is available. It could be considered in patients with high risk disease, but would require funding approval.

**Bortezomib maintenance following HDT**

Bortezomib maintenance improves PFS and OS following HDT in patients receiving PAD induction, compared to VAD induction and thalidomide maintenance (Sonneveld et al 2012). The PFS advantage was also evident in those patients with a t(4;14). Bortezomib together with thalidomide maintenance also improves PFS compared to thalidomide maintenance following induction and HDT (Rosinol et al 2011). Finally the Spanish and Italian myeloma groups have demonstrated benefit of Bortezomib maintenance in elderly patients (Mateos et al 2012, Palumbo et al 2010).

The recommendation is that patients should only receive Bortezomib maintenance in the context of a clinical trial. It could be considered in patients with high risk disease, particularly those with t(4;14), but would require funding approval.

### 4.4 Initial treatment for older, non-HDT candidates

Patients older than 65 years and those less than 65 years who are considered unsuitable for HDT require a different treatment approach. Here chemotherapy is directed at reducing disease burden and myeloma-related organ and tissue impairment.

**Where possible patients should be offered entry in a clinical trial.**

If a patient does not wish to enroll in a clinical trial, the following treatments can be considered.

#### 4.4.1 1st line: MPV

Based on available evidence, bortezomib is recommended as initial treatment for this group of patients. The Phase III VISTA study, comparing melphalan and prednisolone with melphalan, prednisolone and bortezomib (MPV), showed superior response rates in MPV (82 vs. 50%), with CR+VGPR rates of 45% vs. 10%, and superior PFS and OS (3 year OS 72 months vs. 59 months, despite 43% cross-over of patients from the control to the bortezomib arm). Notably, the bortezomib combination was able to overcome the poor prognosis of t(4;14) and del(13q)disease (San Miguel et al, 2008). Two other studies employing MPV in modified schedules have also reported high response rates with the bortezomib combination (Mateos et al, 2010, and Palumbo et al, 2010). These studies reported similar response rates
but with less neurotoxicity (5-6% vs. 13% ≥ grade 3 neuropathy in the VISTA trial), notably as a result of a modified (weekly) bortezomib schedule. Gastro-intestinal toxicities were also less (6 vs. 19%) in these 2 studies. Bortezomib received EU license in 2008, for treatment of newly diagnosed patients over 65 years, in combination with melphalan and prednisolone. Importantly it can be safely administered in renal impairment. An updated follow up of the VISTA study taking into account subsequent therapy for relapse reported maintained survival advantage of patients in the bortezomib arm (median 13.3 months increase in OS (Mateos et al, 2010).

Bortezomib is routinely commissioned by NHS England for first line treatment of multiple myeloma patients for whom transplant is considered unsuitable

**MPV (MELPHALAN/ PREDNISOLONE/ BORTEZOMIB (VELCADE))**

Melphalan 9 mg/m² po once daily, D 1-4
Prednisolone 60mg/m² po once daily, D 1-4
Bortezomib 1.3 mg/m² weekly by sc injection (D1, 8, 15 & 22)
Repeat every 42 days (6 weeks).

REFER TO APPENDIX 6.2.7 FOR SUGGESTED DOSE MODIFICATIONS & SUPPORTIVE CARE. APPENDIX 6.2.3 CONTAINS ADDITIONAL GUIDANCE REGARDING BORTEZOMIB.

**Important Bortezomib toxicity**

- **Peripheral neuropathy, sensory & painful:** usually progressive and variably reversible. Managed by early detection, prompt dose-reductions and good analgesia.
- **Gastrointestinal toxicity:** constipation, diarrhoea, abdominal bloating or pain. Warn patients and have a low threshold for pre-emptive laxative use, or admission for hydration in those with severe diarrhoea, unresponsive to loperamide. These patients are at risk of developing pre-renal acute renal failure.
- **Postural hypotension and pre-syncope secondary to autonomic neuropathy:** consider pre-hydration with saline infusion prior to each dose of bortezomib is a useful prophylactic measure. Screen for pre-syncope and syncope and assess for a postural drop at the start of each treatment cycle. Many patients require dose adjustment of their usual anti-hypertensives for the duration of bortezomib therapy.
- **Thrombocytopenia:** usually progressive over 21-day cycle with recovery prior to next cycle. Check FBC on D1 & D8; consider dose reduction if platelets <30 on D1 and transfuse platelets if <30 on any other treatment day.

For older, more frail patients, when bone marrow reserve is suboptimal, or for those intolerant of MPV, consider bortezomib with low dose cyclophosphamide and prednisolone (VCP):

**VCP (BORTEZOMIB (VELCADE)/CYCLOPHOSPHAMIDE/PREDNISOLONE)**

Cyclophosphamide 50mg orally alt day
Prednisolone 50mg orally alt day
Bortezomib 1.3 mg/m² weekly by sc injection (D1, 8, 15 & 22)
Repeat every 28 days (4 weeks).

REFER TO APPENDIX 6.2.7 FOR SUGGESTED DOSE MODIFICATIONS & SUPPORTIVE CARE. APPENDIX 6.2.3 CONTAINS ADDITIONAL GUIDANCE REGARDING BORTEZOMIB.

**Duration of treatment**

Patients responding should receive up to 8 cycles, assuming there is no unacceptable toxicity.

**4.4.2 2nd line: MPT, CTDa**

The addition of thalidomide to the traditional combination of melphalan and prednisolone has been studied in 6 randomised trials worldwide, with varying schedules and dose intensities, some including maintenance and others treatment for fixed duration. In general, the thalidomide regimen was associated with superior PFS, although the benefit on OS varied across trials. A meta-analysis of around 1600 patients across the 6 trials reported a median survival benefit of 6.6 months (HR 0.83, p<0.004, Fayet et al Blood 2011). Thalidomide has also been studied in the MRC Myeloma IX trial, in the form of CTDa, in comparison with MP. Despite higher response rates, CTDa was not
associated with any benefit in PFS or OS, and was associated with higher rates of thrombosis and neuropathy (Morgan et al, Blood 2011).

For patients less able to attend for therapy on a weekly basis, a thalidomide-containing regimen may be considered as initial therapy in this group of patients. Melphalan/ Prednisolone/ Thalidomide (MPT) should be used, but for patients with poor marrow reserve, or cytopenias, attenuated Cyclophosphamide/ Thalidomide /Dexamethasone(CTDa) is an alternative. Both are well tolerated and administered orally. Thalidomide toxicities may be more significant in this older, frailer patient group and need to be managed pro-actively to maximize delivery of treatment (see appendix 6.2.1, 6.2.2 and 6.2.6 for details regarding toxicity and supportive care).

Decisions about use of thalidomide based regimen compared to bortezomib will depend upon patient choice, frequency of hospital attendances, and whether there is a high risk of VTE. Patients will require anticoagulation with low molecular weight heparin or warfarin.

MPT(MELPHALAN/ PREDNISOLONE/ THALIDOMIDE)
(this is the IFM protocol, which has a higher melphalan dose)
Melphalan 0.25mg/kg* po once daily, D1-4
Prednisolone 2mg/kg po once daily, days 1-4
Thalidomide up to 200 mg (as tolerated) po once daily continuously
Repeat every 42 days (6 weeks).
REFER TO APPENDIX 6.2.6 & 6.2.2 FOR SUGGESTED DOSE MODIFICATIONS & SUPPORTIVE CARE.
*Reduce melphalan to 0.2mg/kg po once daily, D1-4 in patients who are >75years.
Neutrophils must be >1.3x10^9/l and platelets >75x10^9/l prior to commencing treatment (patients with cytopenias should be treated on the CTDa protocol).

CTD/ CTDa (CYCLOPHOSPHAMIDE/ THALIDOMIDE / DEXAMETHASONE(ATTENUATED))
Cyclophosphamide 500 mg po once weekly (D1, 8, 15 & 22)
Thalidomide up to 200 mg (as tolerated) once daily continuously (D1-28)
Dexamethasone 40mg OR 20mg (attenuated) po once daily D1-4 and 15-18*
Repeat every 28 days.
*From cycle 4 reduce dexamethasone to D1-4 only.
REFER TO APPENDIX 6.2.1 & 6.2.2 FOR SUGGESTED DOSE MODIFICATIONS & SUPPORTIVE CARE.

Important thalidomide toxicities
• Venous thromboembolism: highest risk at diagnosis and when combined with conventional chemotherapy or high dose dexamethasone. All patients require a risk assessment to guide thromboprophylaxis (see section 5.3).
• Sensory peripheral neuropathy: this is usually cumulative. It may not resolve for many months following discontinuation of thalidomide. Directed questioning and prompt dose reductions are therefore needed.
• Constipation: laxatives are often required preemptively.
• Haematological toxicity is rare.
• Somnolence: evening dosing minimises this and effect reduces with use.
• Rashes: these are varied and may respond to dose reduction.
• Arrhythmias: known cardiac arrhythmias are a relative contra-indication. Consider cardiology review early in symptomatic patients. Thalidomide is associated with bradycardia.
• Thyroid dysfunction – check baseline thyroid function at start of therapy and re-check every 6 months. Patients on thyroxine supplements should have their thyroid function monitored carefully as dosage may change on thalidomide therapy.

Duration of treatment
If patients are responding, treat for up to 12 cycles if there is ongoing response without unacceptable toxicity.

Maintenance therapy
In older patients receiving conventional chemotherapy (MPT, CTDa, MPV), there is no clear consensus regarding the value of maintenance thalidomide and the toxicity of thalidomide in this patient group may be greater. See section 4.4.3.

Consider single agent thalidomide up to 100mg daily for a further six months in those without contraindications or significant thalidomide-related adverse effects, assuming no adverse cytogenetics (17p deletion).

4.4.3 2nd or 3rd line: Lenalidomide-containing regimens

Patients who do not respond to thalidomide- or bortezomib-containing regimens, or who have contraindications to receiving potentially neurotoxic chemotherapy, should receive a lenalidomide-containing regimen. See Section 4.2.3 for background information and trial data. It is generally well tolerated in older patients but the usual toxicity issues apply.

Lenalidomide should be prescribed with dexamethasone alone, or in conjunction with cyclophosphamide. Have a low threshold for using the “low-dose”, weekly dexamethasone schedule as this has less toxicity (Rajkumar et al, 2010).

LENALIDOMIDE/DEXAMETHASONE

Lenalidomide 25 mg po, D1-21
Dexamethasone 20-40*mg po weekly, D1, 8, 15 and 22 (“low-dose”)

+/–Cyclophosphamide 500 mg po weekly (e.g. D1, 8, 15)
Repeat every 28 days.
*40mg is the standard recommended dose, but 20mg may be used if there is a concern regarding toxicity.
Pulsed dexamethasone may be used if there is need for rapid cytoreduction.
REFER TO APPENDIX 6.2.5 FOR SUGGESTED DOSE MODIFICATIONS & SUPPORTIVE CARE.

Important lenalidomide toxicity

- Cytopenias - regular blood count monitoring is required (2-weekly for first 2 courses at least); patients may need G-CSF.
- Venous thromboembolism – this was significant in the US study (not in the European study), and thromboprophylaxis is recommended (see section 5.3 for risk assessment & recommendations).
- Constipation
- Diarrhoea: this is uncommon but may be troublesome and related to bile acid malabsorption, in which case dietary fat restriction, or use of the bile acid sequestrant, colesevelam may help (Pawlyn et al, 2014)
- Fatigue
- Neuropathy: less frequent than with thalidomide or bortezomib but those with pre-existing neuropathy may develop worsening symptoms.

Duration of treatment

Responding patients should remain on treatment until there is evidence of disease progression or dose-limiting toxicities develop. The drug cost for those who remain on treatment for more than 26 cycles (usually around 2 years) will be met by the manufacturer (Celgene). Dexamethasone doses may be reduced or omitted altogether after 8 cycles.
4.5 Management of relapse from CR or plateau phase

Where possible patients should be entered onto clinical trials.

The alternatives for salvage therapy include a bortezomib, lenalidomide or thalidomide containing regimen. The choice of treatment will depend upon prior therapies, duration of response, previous and/or persistent toxicity from prior therapy, and patient preference (oral vs hospital delivered therapy). In patients who are refractory to bortezomib (either refractory, or have progressed within 60 days of completing therapy) and are either refractory to, or ineligible to receive (due to toxicity) an immunomodulatory agent the prognosis is poor, with a median overall survival of 9 months (Kumar et al 2012). These patients should be considered for next generation agents such as carfilzomib (only licensed in US) and pomalidomide, both of which have shown benefit in this setting. Bendamustine is also available in this setting, and is most commonly used with thalidomide and dexamethasone, or in combination with bortezomib and dexamethasone. Newer agents likely to be licensed in the next 5 years include Carfilzomib (available in the US), panobinostat (HDAC inhibitor), Ixazomib (oral PI) and monoclonal antibodies. All of these newer agents are likely to be effective when used earlier in the disease. All patients should be considered for entry into clinical trials, where possible.

4.5.1 2nd autologous transplant

Younger patients who need treatment for relapsed disease ≥18 months from their first HDT may be eligible for a second ASCT, following cytoreduction. There is emerging data to support the use of a second ASCT in selected patients. Patients treated on the Myeloma X trial demonstrated an improvement in PFS when treated with a second autograft (compared to weekly cyclophosphamide), following PAD re-induction therapy (Cook et al, 2014). A retrospective review of CIBMTR registry data in patients undergoing a second ASCT had a median PFS of 12 months (Michaelsis et al 2013). The median PFS from the first ASCT was 18 months in this registry data. The decision for second ASCT will depend upon the duration from the previous treatment, fitness for second ASCT, availability of stem cells, and what alternative treatment options there are.

4.5.2 Bortezomib-containing regimens

Bortezomib has been approved by NICE (Technology Appraisal guidance 129 – Bortezomib monotherapy for relapsed multiple myeloma; October 2007) for the treatment of patients in first relapse, alongside use of the Velcade Response Scheme (VRS). All such patients should therefore be considered for treatment with bortezomib at first relapse unless considered unsuitable (e.g. with ≥Grade 2 neuropathy).

Patients may benefit from re-treatment with bortezomib if they had previously responded to this agent, especially if they achieved a durable response. In the VISTA trial, patients on the VMP arm who received bortezomib at relapse had a 47% response rate (compared to 59% for those from the MP arm who received bortezomib at relapse), with no significant difference in survival between these 2 groups (Mateos et al 2010a). The phase 2 RETRIEVE study evaluated the outcome of bortezomib re-treatment in patients who responded with at least a PR, and relapsed at least 6 months after initial bortezomib therapy. Overall response rate was 40% with a median TTP of 8.4 months (Petrucci et al 2013).

The recommendation is that patients relapsing at least 6 months from prior bortezomib should be considered for bortezomib re-treatment. In this context, combination with another novel agent (e.g. bendamustine, may improve bortezomib efficacy. Bortezomib re-treatment is funded from the National Cancer Drugs Fund for patients who have achieved at least a PR of at least 6 months duration.

For general and toxicity information regarding bortezomib, see section 4.2.1. Relapsed patients may well have persistent peripheral neuropathy from previous treatments. Treatment with bortezomib may not increase the risk of developing painful sensory neuropathy, although the sensory symptoms may worsen on bortezomib. Subcutaneous bortezomib reduces the incidence and severity of peripheral neuropathy. It is important to monitor these patients carefully.
Bortezomib combinations available
Bortezomib may be given with a variety of other agents, with combinations selected by mode of delivery and toxicity profile.

Weekly Bortezomib (with dexamethasone)
To reduce incidence and severity of bortezomib-related toxicity (neuropathy, gastro-intestinal and fatigue) and for practical convenience of administration, patients should receive bortezomib during their first cycle of treatment. If rapid cytoreduction is required they should receive biweekly bortezomib during their first cycle. Following regimens use 1.3mg/m² SC. There is also data to support using Bortezomib 1.6mg/m² SC weekly.

**WEEKLY BORTEZOMIB/DEXAMETHASON**
Bortezomib 1.3mg/m² SC, D1, 8, 15 & 22
Dexamethasone 20mg po on day of bortezomib injection and day after (i.e. D1, 2, 8, 9, 15, 16, 22 & 23)
Repeat every 5 weeks.

This schedule is well tolerated, and allows the delivery of full dose bortezomib (8 cycles) in most patients. Dose modification may still be necessary in some patients, e.g. with neurotoxicity.

Velcade Response Scheme
The NHS will fund patients at first relapse who achieve a response to Bortezomib (as defined by achievement of ≥ PR after 4 cycles) and Ortho Biotec will provide replacement stock or credit for those patients at first relapse who fail to respond to Bortezomib. Further details for the VRS (and all relevant forms) are available at: [www.velcade.org.uk](http://www.velcade.org.uk)

Alternative regimens including:

**WEEKLY BORTEZOMIB/ CYCLOPHOSHAMIDE/DEXAMETHASONE**
Bortezomib 1.3mg/m² SC, D1, 8, 15 & 22
Dexamethasone 20mg po on day of bortezomib injection and day after (i.e. D1, 2, 8, 9, 15, 16, 22 & 23)
Cyclophosphamide 500mg po days 1, 8, 15, 22
Repeat every 5 weeks.

**PAD (WEEKLY BORTEZOMIB)**
Bortezomib 1.3mg/m² SC, D1, 8, 15 & 22
Doxorubicin 9mg/m²/dayIV bolus injections D1, 2, 3, 4
Dexamethasone 40mg orally, D1-4 (with additional pulses D8-11 & D15-18 in cycle 1)
Repeat every 28 days.

**VTD**
Bortezomib 1.3mg/m² SC, D1, 8, 15 & 22
Thalidomide 100-200mg orally daily
Dexamethasone 20mg po, day of bortezomib & day after (i.e. D1, 2, 8, 9, 15, 16, 22 & 23)
Repeat every 28 days.
**Important Bortezomib toxicity**

- **Peripheral neuropathy, sensory & painful:** usually progressive and variably reversible. Managed by early detection, prompt dose-reductions and good analgesia.
- **Gastrointestinal toxicity:** constipation, diarrhoea, abdominal bloating or pain. Warn patients and have a low threshold for pre-emptive laxative use, or admission for hydration in those with severe diarrhoea, unresponsive to loperamide. These patients are at risk of developing pre-renal acute renal failure.
- **Postural hypotenion and pre-syncope secondary to autonomic neuropathy:** pre-hydration with saline infusion prior to each dose of bortezomib is a useful prophylactic measure. Screen for pre-syncope and syncope and assess for a postural drop at the start of each treatment cycle. Many patients require dose adjustment of their usual anti-hypertensives for the duration of bortezomib therapy.
- **Thrombocytopenia:** usually progressive over 21-day cycle with recovery prior to next cycle, but not usually an issue with 28-day cycles. Check FBC on D1 & D8; consider dose reduction if platelets <30 on D1 and transfuse platelets if <30 on any other treatment day.
- **Fatigue**

### 4.5.3 CTD/CTDa

Patients who have not received thalidomide as part of their induction pre-HDT or initial treatment may be treated with a thalidomide-containing regimen at relapse. It is well tolerated and administered orally. MPT is an alternative in relapse but only in those with demonstrably good bone marrow reserve. Treat as per first-line treatment (section 4.5.2).

**CTD/CTDa (CYCLOPHOSPHAMIDE/ THALIDOMIDE / DEXAMETHASONE(ATTENUATED))**

- Cyclophosphamide 500 mg po once weekly (D1, 8, 15 & 22)
- Thalidomide up to 200 mg (as tolerated) once daily continuously (D1-28)
- Dexamethasone 40mg OR 20mg (attenuated) po once daily D1-4 and 15-18*
  
  *Repeat every 28 days.*
  
  *From cycle 4 reduce dexamethasone to D1-4 only.*

**Important thalidomide toxicities**

- **Venous thromboembolism:** highest risk at diagnosis and when combined with conventional chemotherapy or high dose dexamethasone. All patients require a risk assessment to guide thromboprophylaxis (see section 5.3).
- **Sensory peripheral neuropathy:** this is usually cumulative. It may not resolve for many months following discontinuation of thalidomide. Directed questioning and prompt dose reductions are therefore needed.
- **Constipation:** laxatives are often required preemptively.
- **Haematological toxicity is rare.**
- **Somnolence:** evening dosing minimises this and effect reduces with use.
- **Rashes:** these are varied and may respond to dose reduction.
- **Arrhythmias:** known cardiac arrhythmias are a relative contra-indication. Consider cardiology review early in symptomatic patients.
- **Thyroid dysfunction:** check baseline thyroid function at start of therapy and re-check every 6 months. Patients on thyroxine supplements should have their thyroid function monitored carefully as dosage may change on thalidomide therapy.

Refer to Appendix 6.2.2 for suggested dose modifications & supportive care.

### Duration of treatment

If patients are responding, treat for 6 to 12 cycles if there is ongoing response without unacceptable toxicity.

### Maintenance therapy

Consider single agent thalidomide up to 100mg daily for a further six months in those without contraindications or significant thalidomide-related adverse effects. Discontinue in those achieving CR.

### 4.5.4 Lenalidomide-containing regimen

Lenalidomide has been approved by NICE (Technology Appraisal guidance 171 – Lenalidomide for relapsed multiple myeloma; June 2009) for the treatment of myeloma in patients who have received two or more prior therapies, and...
Bendamustine is a chemotherapeutic agent that combines an alkylator agent with a purine like benzimidazole ring. It is licensed for the treatment of newly diagnosed myeloma patients unsuitable for HDT, who have neuropathy that precludes the use of thalidomide or bortezomib. Bendamustine has clinical activity in relapsed patients, which is where it is mainly used. Although effective as monotherapy, the efficacy is enhanced when combined with steroids and thalidomide, bortezomib or other novel agents.

Outside of clinical trials bendamustine is recommended as a treatment for multiply relapsed patients who have received bortezomib or lenalidomide (or have a contraindication to receiving these agents)(Bendamustine position statement from Myeloma UK/UKMF, Pratt et al, 2013)

Bendamustine treatment is funded from the National Cancer Drugs Fund for patients who have relapsed disease, and where other treatments are contraindicated or inappropriate.

**Bendamustine Dexamethasone**

Bendamustine 60mg/m² IV , D1, 8, +/- 15
Dexamethasone 40mg orally, weekly, D1, 8, 15, 22

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**LENALIDOMIDE/DEXAMETHASONE**

Lenalidomide 25 mg po, D1-21
Dexamethasone 20-40*mg po weekly, D1, 8, 15 and 22 ("low-dose")

+/−Cyclophosphamide 500 mg po weekly (e.g. D1, 8, 15)
Repeat every 28 days.
REFER TO APPENDIX 6.2.5 FOR SUGGESTED DOSE MODIFICATIONS & SUPPORTIVE CARE.
*40mg is the standard recommended dose, but 20mg may be used if there is a concern regarding toxicity. Pulsed dexamethasone may be used if there is need for rapid cytoreduction.

**Important lenalidomide toxicity**

- Cytopenias - regular blood count monitoring is required (2-weekly for first 2 courses at least); patients may needG-CSF.
- Venous thromboembolism – this was significant in the US study (not in the European study), and thromboprophylaxis is recommended (see section 5.3 for risk assessment & recommendations).
- Constipation
- Diarrhoea: this is uncommon but may be troublesome and related to bile acid malabsorption, in which case dietary fat restriction, or use of the bile acid sequestrant, colesvelam may help (Pawlyn et al, 2014)
- Fatigue
- Neuropathy: less frequent than with thalidomide or bortezomib but those with pre-existing neuropathy may develop worsening symptoms.

**Duration of treatment**

Responding patients should remain on treatment until there is evidence of disease progression or dose-limiting toxicities develop. The drug cost for those who remain on treatment for more than 26 cycles (usually around 2 years) will be met by the manufacturer (Celgene). Dexamethasone doses may be reduced or omitted altogether after 8 cycles.

4.5.5  **Newer agents**

**Bendamustine**

Bendamustine is a chemotherapeutic agent for patients who are unsuitable for bortezomib treatment at first relapse, either because they have previously received bortezomib frontline, or due to neuropathy. See section 4.2.3 for background and toxicity information and trial data.

Lenalidomide should be prescribed with dexamethasone alone, or in conjunction with cyclophosphamide.
Repeat every 28 days

Ensure adequate neutrophil count (at least $1 \times 10^9$/L) and platelet count (at least $50 \times 10^9$/L).

**Benadmustine Dexamethasone and Bortezomib**

- Benadmustine 60mg/m$^2$ IV, D1, 8, +/- 15
- Dexamethasone 40mg orally, weekly, D1, 8, 15, 22
- Bortezomib 1.3mg/m$^2$ SC, D1, 8, 15 & 22

*Repeat every 28 days*

**Bendamustine Dexamethasone Thalidomide**

- Bendamustine 60mg/m$^2$ IV, D1, 8, +/- 15
- Dexamethasone 40mg orally, weekly, D1, 8, 15, 22
- Thalidomide up to 100-200mg orally daily

**Carfilzomib**

Carfilzomib is a second generation proteasome inhibitor, that binds irreversibly to the 20S proteosome subunit. It is well tolerated, the commonest toxicities are reversible thrombocytopenia, other cytopenias and fatigue. Significant neurotoxicity is very rare. A phase 2 open label, single arm study (PX-171-003-A1) demonstrated efficacy in patients who were refractory or intolerant to both bortezomib and lenalidomide. Response rate was 23.7% with a median duration of response of 7.8 months, and a median OS of 15.6 months (Siegel et al 2012). This led to FDA approval. The results of a phase 3 study comparing Carfilzomib to Cyclophosphamide and Dexamethasone in patients with multiply relapsed myeloma are awaited (FOCUS trial). The addition of Carfilzomib to Lenalidomide and Dexamethasone significantly improves progression free survival, compared to Lenalidomide and Dexamethasone alone (median 26.3 to 17.3 months, Stewart et al, 2015). Carfilzomib is currently unlicensed in the UK. This is likely to change when more data is available.

**Pomalidomide**

Pomalidomide is an oral immunomodulatory drug, related to thalidomide and lenalidomide. It is well tolerated, the commonest toxicity is neutropaenia, with febrile neutropaenia being unusual. The results of the phase 3 MM-003 trial have been presented recently. Pomalidomide demonstrated efficacy in patients who were refractory to both bortezomib and lenalidomide, and progressed during their last treatment. Patients receiving Pomalidomide and Dexamethasone had an improved PFS (4.0 vs 1.9 months respectively) and OS (12.7 vs 8.1 months) compared to Dexamethasone alone (San Miguel et al 2013). Pomalidomide is funded by the National Cancer Drugs Fund for patients with relapsed/refractory disease who have received bortezomib and lenalidomide therapies.

**Pomalidomide Dexamethasone**

- Pomalidomide 4mg po, D1-21.
- Dexamethasone 40mg orally, weekly, D1, 8, 15, 22

4.5.6 Return to older conventional regimens

Where patients have previously had good responses (remission ≥18months), with durable periods of remission, it may be worth returning to similar regimens, assuming that the toxicity is still manageable.

Options include:

- Cyclophosphamide and dexamethasone alone
- Melphalan and prednisolone alone
4.6 Amyloidosis

Myeloma may be complicated by tissue deposition of amyloid fibrils derived from circulating monoclonal immunoglobulin light chains, leading to multi-organ disease (secondary amyloid). These patients represent a therapeutic challenge - the end organ damage they accumulate impairs their performance status, such that optimal treatment of their myeloma becomes increasingly difficult. Common clinical features include cardiac dysfunction with arrhythmias, liver, renal and bowel involvement and autonomic neuropathy.

In primary (AL) amyloidosis, where the clinical picture is dominated by the multi-organ dysfunction in the absence of overt myeloma, the plasma cell clone is typically small and more often of the lambda-light chain type. Patients with amyloidosis complicating myeloma, as well as those with AL (primary) amyloidosis, have a poor prognosis (e.g. in the Mayo clinic series the median survival was 12-18 months). The main prognostic determinant is amyloid heart disease (NT-proBNP level may be valuable).

The goal of therapy is to achieve at least a free light chain VGPR (defined as dFLC <40 mg/L) as rapidly as possible and early modification of treatment regimes which appear to achieve slow responses is needed in cardiac patients.

Patients suspected of having either form of amyloidosis should be referred to a specialist unit such as the National Amyloidosis Centre at the Royal Free Hospital. They will perform an initial assessment, including SFLCs and a SAP scan. They may make treatment recommendations and will follow up those with confirmed disease after completion of treatment. Contact details are as follows:

Prof. Philip Hawkins, Dr Ashutosh Wechalekar, Dr Julian Gillmore, Dr Helen Lachman
NATIONAL AMYLOIDOSIS CENTRE
Centre for Amyloidosis & Acute Phase Proteins
Department of Medicine
Royal Free Campus, University College London
Royal Free Hospital
Rowland Hill Street, London NW3 2PF

General Enquiries
Tel: 020 7433 2725; Fax: 020 7433 2817
Web: www.ucl.ac.uk/medicine/amyloidosis/

The most effective treatment is high dose chemotherapy with ASCT, aimed at eradicating the plasma cell clone. For patients with AL amyloidosis with significant plasma cell infiltration in the marrow, induction therapy may be required, (e.g. 2 cycles of a dexamethasone-containing regimen) but patients with <10% plasma cells at presentation, can proceed directly for ASCT. Patients considered fit enough for HDT should proceed with GSCF priming (high dose cyclophosphamide should be avoided), HPC-A harvest and ASCT as per protocol for myeloma patients. A split dose melphalan protocol is useful in AL patients and avoids fluid challenge.

Those considered fit enough for high dose steroid but not considered candidates for high dose therapy should receive induction therapy with Cyclo-Velcade-Dex. Patients with neuropathy should be considered for oral melphalan and pulsed dexamethasone or lenalidomide-dexamethasone. Upfront regimes (CTD or MDex) produced significant responses (67% RR, 47 patients) while CVD can give better responses (upto 95% with CR/VGPR in 65%). Caution is needed in using any regime for patients with advanced cardiac amyloidosis (defined as NT-proBNP >1000 pMol/L or SBP <100 mm of Hg in presence of cardiac involvement) especially with bortezomib or thalidomide containing regimes. All patients with Stage III cardiac AL amyloidosis should be considered for admission and starting therapy as inpatients under cardiac monitoring. This particularly so for patients with NT-proBNP >1000 pMol/L and/or SBP <100 mm of Hg/

**WEEKLY BORTEZOMIB/ CYCLOPHOSPHAMIDE/ DEXAMETHASONE**

Bortezomib 1.3mg/m² SC, D1, 8, 15 & 22
Dexamethasone 20mg po on day of bortezomib injection and day after (i.e. D1, 2, 8, 9, 15, 16, 22 & 23)
Cyclophosphamide 500mg po days 1, 8, 15, 22
*Repeat every 5 weeks.*
** Dexamethasone dose should be reduced in patients with severe or uncontrolled cardiac symptoms**

**MELPHALAN AND DEXAMETHASONE**

 Melphalan 0.22mg/kg po once daily, D1-4
 Dexamethasone 40mg po once daily, D1-4
 *Repeat every 28 days, for up to 9 cycles.*

**CTD/CTDa (CYCLOPHOSPHAMIDE/ DEXAMETHASONE(ATTENUATED)/ THALIDOMIDE)**

 Cyclophosphamide 500 mg po once weekly
 Dexamethasone 40mg or 20mg (attenuated) po once daily D1-4 and 15-18 or Days 1,8,15, 22 (for patients with fluid overload or albumin <20g/L)
 Thalidomide – start at 50 mg/d and increase up to 200 mg (as tolerated) once daily continuously. Most patients with amyloidosis do not tolerate thalidomide >100mg/d.
 *Repeat every 28 days, up to 6 cycles.*
 *REFER TO APPENDIX 6.2.2 FOR SUGGESTED DOSE MODIFICATIONS & SUPPORTIVE CARE.*

Response should be assessed by serial SFLC measurement (after every cycle of treatment) and those with measurable paraprotein should also be monitored by paraprotein levels. Treatment should continue until monoclonal protein levels (ideally SFLCs) have plateaued. Discontinue if CR is reached, or for disease progression or toxicity.

Current trials on AL amyloidosis include (EMN-003 for upfront patients, a trial of ixazomib –Dex vs. best standard of care for patients with 1-2 prior regimes). Trials likely to open in 2015/16 include: Carfilzomib dex for upfront treatment, Targeted radiotherapy for transplant eligible patients and Car-Thal-Dex for relapsed disease.

### 4.7 Solitary plasmacytomas

Table 4 below outlines diagnostic criteria that have been drawn up by the International Myeloma Working Group.

<table>
<thead>
<tr>
<th>Table 4. Diagnostic criteria for solitary plasmacytomas</th>
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<tbody>
<tr>
<td><strong>Solitary plasmacytoma of bone (SPB)</strong></td>
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<tr>
<td><strong>Extramedullary plasmacytoma (SEP)</strong></td>
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<td><strong>Multiple solitary plasmacytomas (+/- recurrent)</strong></td>
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*A small M-component may sometimes be present in blood or urine*

Management of solitary plasmacytomas should be directed towards optimal treatment of the index lesion and appropriate follow-up to detect early those who progress to multiple myeloma.

#### 4.7.1 Solitary bone plasmacytoma (SBP)

This is a single area of bone destruction associated with a population of clonal plasma cells, without evidence of systemic disease. They are nearly twice as common in men and most commonly occur in the axial skeleton. Importantly the majority of patients with apparent SBP continue to develop myeloma – 51% within 5 years and 72% within 10 years of diagnosis (Knobel et al, 2006). An abnormal SFLC ratio and the persistence of a monoclonal band for more than one year after radiotherapy predict a higher risk of progression and an adverse overall survival (see table 5). The impact of abnormal cytogenetics in this group is not yet clear.
Table 5. Risk stratification model for SBP progression to myeloma using SFLC ratio and monoclonal protein level

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>RISK GROUP</th>
<th>5 YEAR PROGRESSION RATE</th>
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<tbody>
<tr>
<td>Normal SFLC ratio</td>
<td>Low</td>
<td>13%</td>
</tr>
<tr>
<td>Monoclonal protein &lt;5g/l</td>
<td>Low</td>
<td>13%</td>
</tr>
<tr>
<td>Either variable abnormal</td>
<td>Intermediate</td>
<td>26%</td>
</tr>
<tr>
<td>Abnormal SFLC ratio</td>
<td>Intermediate</td>
<td>26%</td>
</tr>
<tr>
<td>Monoclonal protein &gt;5g/l</td>
<td>High</td>
<td>62%</td>
</tr>
</tbody>
</table>

Derived from Dingli et al, 2006

4.7.1.1 Diagnosis and investigations

- **Histology**: SBP is generally diagnosed by biopsy (FNA is inadequate). Percutaneously guided biopsy of the spine is usually possible by fluoroscopy or CT. As these tumours are rare, a specialist histopathologist should review all these cases (as per NICE guidelines). Monoclonality and/or an aberrant plasma cell phenotype (using CD19, CD56, CD27, CD117 and cyclin D1 expression) must be demonstrated.

- **Baseline blood tests** as per myeloma work-up: no anaemia, hypercalcaemia or renal impairment due to plasma cell dyscrasia; no immune paresis.

- **Serum & urine protein electrophoresis**: absent or low level serum paraprotein and urinary BJP.

- **SFLCs**: perform at baseline for prognostication

- **BM aspirate & trephine**: normal.

- **Skeletal survey**: (including radiographs of long bones): normal apart from index lesion.

- **MRI whole spine & pelvis**: no additional lesions.

CT/PET has the advantage of imaging the whole body and as such may identify other lesions (especially extramedullary) not seen on MRI. However it remains investigational and is not yet validated as a mandatory part of SBP staging.

4.7.1.2 Treatment

**Radical radiotherapy**

This remains the treatment of choice for SBP.

- For SBP up to 5cm diameter, radical radiotherapy (40 Gy in 20 fractions) to the tumour, encompassing the tumour volume shown on MRI with a margin of at least 2cm, is recommended.

- For bulky SBP (>5cm), a higher dose of 45-50 Gy in 20-25 fractions is recommended; alternatively combined modality treatment with chemotherapy may be used.

- Patients who present as apparent SBP but found to have more extensive disease on MRI should be considered to have myeloma and treated accordingly.

**Surgery**

This is indicated only to treat complications of SBP, e.g. pain, vertebral instability or neurological compromise. An early neurosurgical opinion is recommended. It is generally recommended that surgery should precede radiotherapy, because surgery is technically more difficult after radiotherapy. Prior surgery may however compromise radiotherapy, e.g. placing of metal supports, so close liaison between surgical, haematological and radiotherapy teams is essential. Surgery should never be considered as sole treatment of SBP.

**Follow up & Role of Chemotherapy**

Following radiotherapy, patients should be monitored 6-8 weekly for 6 months with FBC, U&E, serum calcium, immunoglobulins and monoclonal protein quantification (serum paraprotein, urine Bence Jones protein or SFLC). Thereafter follow up intervals may be extended.

Patients who do not respond to radiotherapy should be treated with chemotherapy as for myeloma, including consolidation with high dose therapy for suitable patients. Patients who relapse with bone marrow involvement should be treated as for myeloma. In some cases of plasmacytoma, relapse may take the form of a new solitary lesion in a different site to the index lesion. If this is a true unifocal relapse (CT-PET scanning may be helpful in these cases), it is worth considering further local radiotherapy and deferring systemic therapy until there is clear evidence of myeloma, with bone marrow involvement and multiple lytic lesions.
4.7.2 Solitary extramedullary plasmacytoma (SEP)

Extramedullary (soft tissue) plasmacytoma (SEP) are less common than SBP and represent soft tissue infiltration by clonal plasma cells. They may arise anywhere in the body, but >90% arise in the head and neck, especially the upper respiratory tract. Typically they remain localized, are potentially curable with radiotherapy and rarely progress to myeloma.

4.7.2.1 Diagnosis and investigations

- **Histology**: this is usually diagnostic, confirming tissue infiltration by clonal (i.e. not reactive) plasma cells, usually with an aberrant phenotype (as with SBP). They must be distinguished from clonal B-cells (i.e. lymphoma). Once again, it is essential that these biopsies are reviewed by specialist histopathologists.

- **Baseline blood tests** as per myeloma work-up: no anaemia, hypercalcaemia or renal impairment due to plasma cell dyscrasia; no immune paresis.

- **Serum & urine protein electrophoresis**: absent or low level serum paraprotein and urinary BJP.

- **SFLCs**: perform at baseline for prognostication, although their role is less clear than in SBP.

- **BM aspirate & trephine**: normal.

- **Skeletal survey (including radiographs of long bones)**: normal.

There is little evidence that MRI can detect occult lesions elsewhere, such as the spine, so this is not recommended. CT/PET may identify other asymptomatic lesions but its role in routine work-up is not yet clear.

4.7.2.2 Treatment

**Radical radiotherapy**

This usually produces excellent local disease control and long-term disease free survival.

- Radical radiotherapy to the tumour, encompassing the primary tumour with a margin of at least 2cm, is recommended.

- The cervical nodes should be included if involved. The first echelon cervical node should be included in SEP of Waldeyer’s ring.

- Those up to 5cm require 40 Gy in 20 fractions, whereas larger SEP >5cm require up to 50 Gy in 25 fractions.

**Surgery**

Radical surgery should be avoided in the head and neck as it may be disfiguring and the tumour is usually very responsive to radiotherapy. For SEP at other sites (e.g. GI tract), complete surgical removal should be considered if feasible, but patients with involved surgical margins should receive adjuvant radiotherapy.

**Follow up & Role of Chemotherapy**

Patients with SEP should be monitored 6-8 weekly for 6 months to detect progression to myeloma, extending clinic appointment intervals thereafter. Monitoring should include clinical assessment as well as FBC, U&E, serum calcium and quantification of monoclonal protein (serum paraprotein, urine Bence Jones protein or SFLC).

Adjuvant chemotherapy should be considered in patients with tumours >5cm or those of high grade. Patients who do not respond to radiotherapy or relapse after initial response should be treated with chemotherapy as for myeloma, including consolidation with high dose therapy for suitable patients.
5 Supportive care

5.1 Bone disease

5.1.1 Bisphosphonates

Pamidronate and sodium clodronate both reduce skeletal related events (SRE) compared to placebo in patients with symptomatic myeloma (irrespective of bone disease at diagnosis). The Myeloma IX trial reported a significant reduction in SRE, and improvement in PFS and OS compared to sodium clodronate in newly diagnosed patients with symptomatic myeloma (Morgan et al 2012).

Based on this evidence all patients with myeloma requiring treatment should receive bisphosphonates, irrespective of whether they have bone lesions.

- Newly diagnosed patients should receive Zoledronic acid, due to its superior efficacy.
- Patients unable to receive Zoledronic acid, should receive either Pamidronate or Sodium Clodronate depending upon physician or patient choice.
- Patients should be counselled about possible (low) risk of ONJ, have dental problems identified and a formal dental assessment should be considered in all patients commencing bisphosphonates (especially intravenous). Do not delay starting treatment in those with bone disease, pending dental review.
- Duration of treatment is unknown. Bisphosphonates should be continued at least until patients are in a stable plateau phase. The frequency of administration of intravenous bisphosphonates may be reduced after this period.
- During HDT, most patients will have bisphosphonates discontinued and should be recommenced 6 months post-ASCT.
- Patients intolerant of Sodium Clodronate should receive Pamidronate 90mg IV every 3 to 4 months.
- Relapsed patients with active bone disease should re-commence a bisphosphonate.

Monitoring of renal function is required as adjustments in dosage or infusion times may be needed with renal impairment. Current manufacturers’ guidance follows:

- Sodium clodronate: halve dose if creatinine clearance 10-30ml/min; contraindicated if <10ml/min.
- Pamidronate: reduce infusion rate to 20mg/hour in mild-moderate renal impairment (30-90ml/min); if creatinine clearance <30ml/min, give cautiously at reduced infusion rate and with frequent monitoring of renal function.
- Zoledronic acid: check creatinine and assess/supplement hydration before each infusion; do not give if creatinine >265µmol/l.

Monitor serum calcium levels and vitamin D3 levels and administer calcium supplements in patients with hypocalcaemia, especially if accompanied by raised parathyroid hormone (PTH) levels. It is worth noting that patients with resistant hypercalcaemia may achieve better control of their calcium levels on clodronate.

There is no evidence to support bisphosphonate use in patients with asymptomatic myeloma.

5.1.2 Bone pain & pathological fractures

Myeloma bone disease may cause significant pain without pathological fractures. It occurs most commonly in the axial skeleton but can affect any site. Systemic therapy should help in all sites but additional measures may need to be considered in patients with severe pain symptoms or concerns over high fracture risk, especially involving the vertebral column. For management of suspected or confirmed acute spinal cord compression, see section 3.2. Any lesions with possible instability should be reviewed by the neurosurgical or orthopaedic teams. Complex or resistant cases of bone pain should be referred early to pain management teams.

5.1.2.1 Radiotherapy

Pain arising from both skeletal and soft tissue disease can be effectively treated with local radiotherapy. It may be combined with systemic therapy and the radiation doses required are usually low, with minimal toxicity. It is therefore useful at all disease stages, especially in the terminal phases where palliation is the prime goal.

Large lytic lesions may be irradiated to promote healing and minimise the risk of pathological fracture.
5.1.2.2 Surgery
Vertebral fractures with associated instability or spinal cord compromise require urgent neurosurgical assessment (see section 3.2). Long bone fractures require surgical stabilization with post-operative local radiotherapy to treat disease and promote healing.

5.1.2.3 Vertebroplasty & Kyphoplasty
Vertebroplasty is a radiological intervention which involves the percutaneous injection of polymethacrylate (a type of bone cement) into a damaged vertebral body to relieve pain, strengthen bone and reduce the risk of further collapse at that level. It may be used at one or more vertebral levels simultaneously. It gives demonstrable benefits in terms of pain and mobility but cannot restore vertebral height (Diamond et al, 2004).

In kyphoplasty a needle is inserted percutaneously into the collapsed vertebral body and through this is passed an inflatable balloon. Inflating this restores the vertebral height. The balloon is then removed and the space created is filled with bone cement. The potential benefits are therefore pain relief, improved mobility and some restoration of the vertebral anatomy.

The most common complications are cement leakage and acute fractures. NICE made the following recommendations in 2006 (IPG166; published January 2008):

- Vertebraplasty or kyphoplasty should be considered for patients who have vertebral metastases and no evidence of musculoskeletal spinal cord compression or spinal instability if they have either:
  - mechanical pain resistant to analgesia, or
  - vertebral body collapse
- Vertebraplasty or kyphoplasty for spinal metastases should only be performed after agreement between appropriate specialists including an oncologist, interventional radiologist, and spinal surgeon, and in facilities where there is good access to spinal surgery.

Either intervention may be considered in patients with severe focal pain persisting for more than six weeks after acute vertebral fracture.

5.2 Infections & antimicrobials
Increased tendency towards infection is a defining feature of myeloma and can be attributed to disease-related factors (B-cell defects, hypogammaglobulinaemia and altered T-cell function) and treatment-related factors (neutropaenia, high-dose steroids).

Management of acute infections
- All febrile patients require prompt treatment with broad-spectrum antibiotics that will cover *S. pneumoniae, H. influenzae* and *E. coli*. There should be a lower threshold for treatment with intravenous antibiotics.
- Aminoglycosides should be used with caution, even in those with apparently normal renal function.
- Please use myeloma-specific neutropaenic antibiotic protocols (usually without aminoglycosides).

Use of growth factors
There are no myeloma chemotherapy regimens that require growth factor use as standard from cycle 1. Nadir counts done for the first cycle may guide practice. Patients developing treatment-related neutropaenia should be dose-reduced in the first instance, especially if receiving induction treatment. Stem cell harvesting may be compromised. Patients who suffer recurrent infections in the context of treatment-related neutropaenia may benefit from GCSF.

Antimicrobial prophylaxis
Routine prophylactic use of antibiotics or IVIG in patients with myeloma not receiving chemotherapy is discouraged. However those on treatment may require specific antimicrobial prophylaxis.

- Anti-viral prophylaxis with aciclovir 200mg po tds is recommended for all those receiving treatment. This should continue for at least 3 months post HDT.
Pneumocystis carinii pneumonia (PCP) prophylaxis is recommended for all those receiving high-dose steroids in the context of induction therapy pre-HDT. Older patients who are not HDT candidates do not require PCP prophylaxis. Options include oral co-trimoxazole 960mg po bd three times weekly, dapsone 100mg daily or nebulised pentamidine 300mg monthly. Those receiving CD34-selected stem cells as part of their high-dose therapy should have nebulised pentamidine prior to hospital discharge, converting to oral co-trimoxazole at outpatient review 6 weeks following high dose therapy, if blood counts permit (otherwise continuing nebulised pentamidine). This should continue until the CD4 count reaches >0.4x10^9/L.

Patients with evidence or history of previous hepatitis B infection may need lamivudine (100mg od orally) prophylaxis when on chemotherapy and for 6 months afterwards. Patients with past or chronic hepatitis C infection should be discussed with a hepatologist before commencing chemotherapy.

Patients with recurrent debilitating infections may be considered for penicillin/erythromycin prophylaxis according to infection sites.

IV immunoglobulin (0.4g/kg monthly) may be considered in those patients with life threatening infections or recurrent infections despite antibiotic prophylaxis; renal function should be monitored since there are reports of deterioration with IVIG.

Vaccination
Vaccination against influenza, Streptococcus pneumonia and Haemophilus influenza is recommended, although only the Hib vaccine has been shown to result in useful protective antibody titres (compared to those seen in a healthy population).

5.3 Thromboprophylaxis

Myeloma and other plasma cell disorders have a well-established association with venous thromboembolism (VTE). The age and sex-adjusted incidence of VTE is >1% annually, increasing to >7% in cancer patients. Thalidomide and lenalidomide have been demonstrated to further increase this risk and numerous thromboprophylactic strategies have been used to tackle this. Importantly neither drug used as monotherapy significantly increases risk, but when combined with high-dose steroids or cytotoxic agents the risk of VTE increases from 3-4% to 14-26% (both thalidomide and lenalidomide).

All myeloma patients starting thalidomide or lenalidomide should undergo a risk assessment for venous thromboembolism (see appendix 6.5 for a suggested risk assessment proforma). This assessment needs to take into consideration patient factors (e.g. previous VTE, obesity, co-morbidities), myeloma factors (e.g. at diagnosis (when risk is higher than at relapse), hyperviscosity) and treatment factors (e.g. concurrent use of high-dose steroids). It is recommended that centers use a risk assessment proforma as a formal documentation of the process. Patients taking hormone replacement therapy should be encouraged to discontinue it where possible.

Patients on thalidomide or lenalidomide monotherapy do not require thromboprophylaxis if they have no additional risk factors (Palumbo et al, 2008). Those on lenalidomide with 1 additional risk factor may receive aspirin 75mg once daily but there is no evidence that this is protective for a similar group on thalidomide. The latter require greater protection in the form of prophylactic-dose low molecular weight heparin (LMWH) (e.g. dalteparin 5000units once daily SC or equivalent). Those with 2 additional risk factors require prophylactic-dose LMWH (e.g. dalteparin 5000units once daily SC). Those with 3 or more risk factors need full anticoagulation with either treatment-dose LMWH or warfarin with target INR of 2.5. There is no evidence of benefit with fixed low-dose warfarin or using target INR less than 2. These recommendations and relevant risk factors are summarized in table 6.

LMWH is preferable to warfarin in most cases. In the treatment of VTE in cancer patients, it is less frequently associated with either bleeding or recurrent VTE (Lopez et al, 2004). In the prophylactic setting, it does not require monitoring of anticoagulant effect, and can be quickly adjusted in the face of falling platelet counts or other complications of treatment. Patients who do not tolerate daily injections or those with severe renal impairment may receive warfarin but achieving therapeutic INRs may be difficult in the context of multiple potential drug interactions. Those starting LMWH should have a baseline platelet count and then further platelet counts every 2 to 4 days for the first 2 weeks of treatment, to screen for heparin-induced thrombocytopenia (HIT) (with a platelet count also at 24 hours if the patient has received heparin (unfractionated or LMWH in the previous 100 days). Do not use LMWH in any patients with heparin hypersensitivity or a history of HIT. For patients weighing >100kg, treatment
dose dalteparin may need to be dose adjusted, given in divided doses and monitored with anti-Xa levels. Patients with renal impairment (CrCl <30ml/mins) have more unpredictable responses to LMWH; consider dose reduction (e.g. dalteparin2500units od for prophylaxis) and monitoring with anti-Xa levels. Some patients may benefit from use of a novel oral anticoagulant, depending on availability and physician choice.

Table 6. Summary of thromboprophylaxis recommendations for patients receiving thalidomide or lenalidomide.

<table>
<thead>
<tr>
<th>Additional risk factors *</th>
<th>Risk level</th>
<th>Suggested thromboprophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LOW</td>
<td>Aspirin (enteric coated) 75mg/day (lenalidomide ONLY) OR Dalteparin 5000units** od SC</td>
</tr>
<tr>
<td>2 or more</td>
<td>MODERATE</td>
<td>Dalteparin 5000units** od SC</td>
</tr>
<tr>
<td>3 or more</td>
<td>HIGH</td>
<td>Dalteparin 200units/kg od SC(maximum 18,000units) OR warfarin (target INR 2.5)</td>
</tr>
</tbody>
</table>

*Individual risk factors
- Obesity (BMI ≥30)
- Immobility
- Personal history of VTE – **NB. This counts as 2 risk factors**
- Family history of VTE
- Thrombophilias (inc. antiphospholipid syndrome), myeloproliferative disorders, haemoglobinopathies
- Central venous catheter or pacemaker
- Co-morbidities: cardiac disease, chronic renal disease & nephrotic syndrome, diabetes, acute infection, chronic inflammatory disease (e.g. rheumatoid arthritis, inflammatory bowel disease)
- Surgery: neurosurgery, trauma, orthopaedic > general surgery, any anaesthesia
- Medications: erythropoietin, hormone replacement therapy, tamoxifen, stilboestrol

Myeloma-related risk factors
- At diagnosis
- Hyperviscosity

Myeloma therapy (in addition to lenalidomide or thalidomide)
- High-dose steroids (dexamethasone ≥480mg/month or equivalent)
- Doxorubicin
- Combination chemotherapy

**this may need to be reduced in
- Patients with renal impairment (CrCl <30ml/min) should receive dalteparin 2500units od.
- Patients <45kg or >100kg – discuss with haemostasis team.

Adapted from Palumbo et al, 2008

Thrombocytopenia is a frequent obstacle to safe thromboprophylaxis, related to both marrow infiltration and myeloma treatment. Patients with platelet counts <100 x10^9/l need to be monitored closely and if the platelet count falls below 50 x10^9/l, thromboprophylaxis should be paused, except in very high-risk cases which should be discussed with a haemostasis expert. Always consider the important albeit rare possibility of HIT in those on LMWH, with sudden platelet falls of >50% from baseline within 2 weeks of starting LMWH.

Duration of thromboprophylaxis remains contentious. Clearly the risk of VTE falls as disease burden decreases and the majority of VTE in myeloma patients occur within the first 6 months of treatment. Thromboprophylaxis should therefore be given for at least the first 4 to 6 months of treatment and may then be de-escalated or discontinued unless there are ongoing significant risk factors.

Bleeding is a major concern and thrombocytopenia and concurrent medication may increase this risk. Additionally some patients with myeloma develop coagulopathic states related to hypo- and dys-fibrinogenemia, with unpredictable effects on bleeding risk. However, generally those on aspirin or prophylactic-dose LMWH have very low incidence of major bleeding. Where therapeutic dose LMWH is required and the patient is felt to be at increased risk, the LMWH should be given in divided doses (i.e. 12 hourly). Mechanical thromboprophylactic measures (e.g. graduated elastic compression stockings) are a useful adjunct to pharmacological measures, although patients must be screened for any contraindications to use (e.g. severe peripheral vascular disease). All patients should receive peptic ulcer prophylaxis. Complex cases should be discussed with a specialist haemostasis consultant.
Other patients not receiving thalidomide or lenalidomide may also be at risk of VTE for various reasons and thromboprophylaxis may be appropriate. This is particularly true of those admitted for management of acute episodes (infection, dehydration, pain management), where their risk of thrombosis may increase dramatically. These patients need to be considered on a case-by-case basis and specific recommendations cannot be made.

5.4 Anaemia & erythropoietin

Anaemia is common in patients with myeloma at diagnosis, and is likely to be multifactorial, resulting from bone marrow infiltration, renal impairment and also a dilutional effect of the paraprotein. A positive Direct AntiglobulinTest (DAT) is not uncommon, but is not usually associated with a clinically significant degree of haemolysis. The degree of anaemia can be out of proportion to the level of bone marrow involvement.

- Patients with moderate to severe renal impairment should receive erythropoietin support according to the protocol for renal patients; this is usually done in conjunction with the renal team.

Patients with symptomatic anaemia (Hb <10 g/dl) and who are on chemotherapy should be given a trial of erythropoiesis-stimulating agents (ESA), e.g. epoitoen alfa or beta or darbepoietin (particularly in patients with renal impairment).

- Serum erythropoietin levels may be measured before treatment as those with >200 IU/ml as less likely to respond. Those with severe anaemia (Hb <9 g/dl), high transfusion requirements (>1 unit/ month) and thrombocytopenia (<100 x10⁹/l) are also less likely to respond.
- Check and correct iron,B12 and folate levels prior to starting ESAs.
- Start with 30,000U of epoietin beta (NeoRecormon) SC once weekly.
- Double dose if no signs of benefit after 4-6 weeks.
- Stop EPO if Hb has not risen by 1-2 g/dl after 6-8 weeks.
- Either stop EPO or reduce dose once Hb >12 g/dl.

Patients with symptomatic anaemia who are not receiving chemotherapy may be considered for EPO, although there is less evidence of benefit in this group.

5.5 Painful peripheral neuropathy

5.5.1 Assessment of painful peripheral neuropathy

Assessment and careful documentation of neuropathic symptoms is important to allow accurate monitoring and guide management decisions, such as dose reduction. Remember to check for other common causes of peripheral neuropathy such as vitamin B12 deficiency or diabetes.

Different forms of neuropathic pain exist and distinguishing them is important in tracking any progression. *Allodynia:* Painful response to normally non-noxious stimuli
*Tactile allodynia:* Painful response to normally non-noxious touch
*Hyperalgesia:* Exaggerated painful response to normally noxious stimuli
*Thermal hyperalgesia:* Exaggerated painful response to normally noxious temperatures
*Mechanical hyperalgesia:* Exaggerated painful response to normally noxious body movement

Document any neuropathy symptoms carefully, grading symptoms (see table 7). This should be done before patients commence thalidomide or bortezomib therapy, when stopping treatment, when new neurological symptoms develop and at each review as appropriate.

<table>
<thead>
<tr>
<th>Table 7. Grading of severity of painful peripheral neuropathy (CTC criteria)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severity of Peripheral neuropathy</strong></td>
</tr>
<tr>
<td>Grade 1</td>
</tr>
<tr>
<td>Grade 2</td>
</tr>
<tr>
<td>Grade 3</td>
</tr>
<tr>
<td>Grade 4</td>
</tr>
</tbody>
</table>
Psychological assessment
It is important at initial assessment to determine if there is likely to be a depressive element, as depression can greatly affect an individual’s response to, and ability to cope with, pain. Such patients should be started on a tricyclic antidepressant such as amitriptyline or imipramine initially and perhaps referred for counseling, or for complementary therapy.

Referral to Neurology
Patients who develop severe (grade 3 or above) or atypical neuropathy should be discussed and/or referred to neurology. They may recommend or arrange a number of further investigations, including nerve conduction studies, CSF analysis, anti-neuronal antibodies, gadolinium-enhanced MRI of spine/plexii, nerve biopsy.

Where neuropathy develops in the context of renal impairment, arrhythmias, gastrointestinal symptoms or heart failure, consider referring to the National Amyloidosis Centre for exclusion of amyloidosis.

5.5.2 Management of painful peripheral neuropathy
Dose adjustment
If related to bortezomib, adjust dose as per appendix 6.2.4. For thalidomide neuropathy, see appendix 6.2.3.

Drug treatment
Involve pain management specialists early, for example if patients are not responding to first line analgesia. The following algorithm (Table 8) may be used according to availability of drugs on local formulary. Topical capsaicin cream (e.g. Axsain cream – 0.075% capsaicin) may also be helpful.

Table 8. Recommended algorithm for neuropathic pain

<table>
<thead>
<tr>
<th>Line</th>
<th>Dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>Gabapentin 300mg tds, escalated to 900mg tds (alternatively, pregabalin 75mg bd, escalated slowly up to 300mg bd maximum) OR Amitriptyline 10-50 mg nocte (alternatively, duloxetine 60mg od)</td>
</tr>
<tr>
<td>2nd</td>
<td>Gabapentin (or pregabalin) AND amitriptyline (or duloxetine)</td>
</tr>
<tr>
<td>3rd</td>
<td>Oxycodone OR methadone, either alone or in combination with gabapentin</td>
</tr>
<tr>
<td>4th</td>
<td>Only on advice from a specialist team</td>
</tr>
</tbody>
</table>

Complementary approaches
The evidence base for these is lacking but there is anecdotal evidence that some patients may benefit. Consider referral to local Complementary Therapy Teams. Aromatherapy, foot massage, reflexology, Reiki and counselling have all been shown to be beneficial in some cases. Additional empirical measures useful in some cases are summarised in table 9.

Table 9. Complementary approaches to neuropathy

<table>
<thead>
<tr>
<th>Vitamin supplements</th>
<th>B12: 400mcg daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B6: 50mg qds</td>
</tr>
<tr>
<td></td>
<td>Folic acid: 1 to 2 mg daily</td>
</tr>
<tr>
<td></td>
<td>Vitamin E: 400 IU daily or topical applications through twice-daily cocoa butter massages</td>
</tr>
<tr>
<td>Other supplements</td>
<td>Tonic Water</td>
</tr>
<tr>
<td></td>
<td>Mg supplements</td>
</tr>
<tr>
<td></td>
<td>Acetyl-L-Carnitine 400mg to 500mg bd</td>
</tr>
<tr>
<td></td>
<td>Alpha Lipoic Acid 200mg to 400mg bd</td>
</tr>
<tr>
<td></td>
<td>Evening primrose oil</td>
</tr>
<tr>
<td>Other interventions</td>
<td>Exercise: active and passive forms may reduce cramps, improve muscle strength, and prevent muscle wasting in affected limbs.</td>
</tr>
<tr>
<td></td>
<td>Stop smoking: particularly important as may contribute to ischaemic neuropathy and worsen symptoms.</td>
</tr>
<tr>
<td></td>
<td>Self-care skills, e.g. meticulous foot care, careful wound treatment, where there is impaired ability to feel pain.</td>
</tr>
<tr>
<td></td>
<td>Assistive Devices: Hand or foot braces can compensate for muscle weakness or alleviate nerve compression. Orthopaedic shoes can improve gait disturbances and help prevent foot injuries in people with a loss of pain sensation.</td>
</tr>
</tbody>
</table>
5.6 Tumour lysis prevention

Tumour lysis syndrome is relatively rare in myeloma due to the low proliferative rate of the malignant cells. However the increased susceptibility to renal injury in this patient group necessitates appropriate preventative strategies.

All patients should receive allopurinol 300mg od orally for their first cycle of chemotherapy. Consider extending this to first 2-3 cycles in those with heavy disease infiltration at presentation (high paraprotein, heavy marrow infiltration on trephine). Those with impaired renal function may need dose reducing.

Rapid cytoreduction may occur when commencing bortezomib treatment and several case series highlight this problem. There is very little experience with rasburicase in this setting, hence recommendations cannot be made.
6 Appendices

6.1 Response criteria

These have been modified and we now use the International uniform response criteria for multiple myeloma (Kyle RA and Rajkumar SV, 2009).

Major changes from the EBMT criteria are:

- **Stringent CR (sCR)**
  CR as defined below plus Normal FLC ratio and Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence

- **Complete Response (CR)**
  Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤5% plasma cells in bone marrow, also requires no increase in size or number of lytic bone lesions

- **Very Good Partial response (VGPR)**
  Serum and/or urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum paraprotein plus urine light chain level < 0.1g / 24 h.

- **Partial Response (PR)**
  ≥50% reduction of serum paraprotein and reduction in 24hr urinary light chain by ≥90% or to ≤200 mg per 24hr. If the serum and urine light chains are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required

- **Stable Disease (SD)**
  Not meeting criteria for CR, VGPR, PR or progressive disease

- **Progressive Disease**
  Progressive disease requires any one or more of the following:
  - Increase of ≥ 25% from baseline in the serum paraprotein (absolute increase must be ≥5 g/l) and/or urine light chains (absolute increase must be ≥0.2g/24h)
  - Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be 410 mg/dl.
  - Bone marrow plasma cell percentage: the absolute % must be X 10%
  - Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
  - Development of hypercalcaemia (corrected serum calcium 411.5 mg/dl or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder

6.2 Chemotherapy regimens

6.2.1 CTD/CTDa*

Cyclophosphamide 500mg po once weekly
Dexamethasone 40mg* po once daily days 1-4, and 15-18**
Thalidomide 100-200 mg po once daily continuously
28 day cycle.
*For older patients, use CTDa (attenuated) with dexamethasone dose reduced to 20mg
**After first 3 cycles, reduce dexamethasone to days 1-4 only**

The number of cycles of CTD will depend on the stage in their treatment and the response of the patient.

For dosing information, dose modifications & additional information on Thalidomide, see appendix 6.2.3.

**Supportive Care**
- Stress-ulcer prophylaxis
- Aciclovir 200mg tds po
- Co-trimoxazole 960mg od Mon/Wed/Fri po
- Allopurinol 300mg od po for at least first cycle, up to cycle 3 if heavy disease burden.
- Thromboprophylaxis – see section 5.3.
- Laxatives
- Anti-emetics

**Suggested Dose Modifications**

**Renal Impairment:**

<table>
<thead>
<tr>
<th>Creatinine (mmol/L)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;300</td>
<td>100%</td>
</tr>
<tr>
<td>300-600</td>
<td>50%</td>
</tr>
<tr>
<td>&gt;600</td>
<td>Omit; dialysed patients may receive same dose as for creatinine 300-600</td>
</tr>
</tbody>
</table>

**6.2.2 Thalidomide**

Thalidomide 100-200mg once daily po, continuously.

This may need to be introduced gradually to minimise toxicity in those without prior exposure, i.e. 50mg once daily for 2 weeks, then 100mg once daily for 2 weeks, increasing up to a maximum of 200mg once daily by 50mg intervals. Usually given in combination, i.e. with cyclophosphamide and dexamethasone (CTD/CTDa; appendix 6.2.2) or with melphalan and prednisolone (MPT; appendix 6.2.8). It may be given as monotherapy in maintenance setting (usual maximum dose of 100mg).

**Important toxicities**
- **Venous thromboembolism:** highest risk at diagnosis and when combined with conventional chemotherapy or high dose dexamethasone. All patients require a risk assessment to guide thromboprophylaxis (see section 5.3).
- **Constipation:** laxatives are often required preemptively.
- **Sensory peripheral neuropathy:** this is usually cumulative. It may not resolve for many months following discontinuation of thalidomide. Directed questioning and prompt dose reductions are therefore needed.
- **Haematological toxicity is rare.**
- **Somnolence:** evening dosing minimises this and effect reduces with use.
- **Rashes:** these are varied and may respond to dose reduction.
- **Arrhythmias:** known cardiac arrhythmias are a relative contra-indication. Consider cardiology review early in symptomatic patients.
- **Thyroid dysfunction:** check baseline thyroid function at start of therapy and re-check every 6 months. Patients on thyroxine supplements should have their thyroid function monitored carefully as dosage may change on thalidomide therapy.
- **Congenital malformations due to foetal exposure:** there have been no reported cases of birth defects in myeloma patients on thalidomide. Pharmion RMP protocols are in place to minimise the risks.

The manufacturers of thalidomide, Pharmion, have developed a risk management programme, which includes patient information, consent documents and appropriate counseling and dispensing checklists. This material should be used in all cases.

**Supportive care**
- Thromboprophylaxis – see section 5.3.
• Laxatives

Suggested dose modifications
For toxicity G1 or 2, consider pausing thalidomide treatment (e.g. for 1 week) and then resuming at 50% previous dose level. If this is tolerated and toxicity does not return, consider gradually increasing to previous dose level. If toxicity returns or is G3 or 4, thalidomide may need to be stopped completely.

6.2.3 BCD

- Bortezomib 1.3mg/m² sc bolus, D1, 8, 15 and 22
- Cyclophosphamide 500mg po, weekly (e.g. D1, 8 and 15)
- Dexamethasone 20mg po, day of bortezomib & day after (i.e. D1, 2, 8, 9, 15, 16, 22 & 23)

Repeat every 28-35 days, for up to 8 cycles.

Patients with cytopenias should be started on bortezomib and dexamethasone only.

Bortezomib is given by subcutaneous injection. Sub cutaneous vs intravenous bortezomib is associated with a reduction in neuropathy and other side effects. For patients intolerant of sc injection, bortezomib can be given as a rapid intravenous injection (over 3-5 seconds). There must be a gap of at least 72 hours between doses.

Patients achieving a complete response (CR) should receive 2 additional cycles following confirmation of response. Patients achieving a partial response (PR) should receive 2 cycles after reaching a plateau, up to a maximum of 8 cycles, to consolidate response.

If rapid cytoreduction is required consider biweekly 21 day schedule. This is usually only required for 1 or 2 cycles.

- Bortezomib 1.3mg/m² IV bolus, D1, 4, 8 & 11
- Cyclophosphamide 500mg po, weekly, e.g. D1, 8, 15
- Dexamethasone 20mg po, day of bortezomib & day after (i.e. D1, 2, 4, 5, 8, 9, 11 & 12)

Repeat every 21 days

Supportive Care
• Stress-ulcer prophylaxis
• Aciclovir 200mg tds po
• Co-trimoxazole 960mg od Mon/Wed/Fri po; not necessary for patients post-autograft or not candidates for HDT
• Allopurinol 300mg od po for at least first cycle, up to cycle 3 if heavy disease burden.
• Anti-emetics

Major toxicities
• Peripheral neuropathy, sensory & painful: usually progressive and variably reversible. Managed by early detection, prompt dose-reductions and good analgesia (see below).
• Gastrointestinal toxicity: constipation, diarrhoea, abdominal bloating or pain. Warn patients and have a low threshold for pre-emptive laxative use, or admission for hydration in those with severe diarrhoea, unresponsive to loperamide. These patients are at risk of developing pre-renal acute renal failure.
• Postural hypotension and pre-syncpe secondary to autonomic neuropathy: pre-hydration with saline infusion prior to each dose of bortezomib is a useful prophylactic measure. Screen for pre-syncpe and syncope and assess for a postural drop at the start of each treatment cycle. Many patients require dose adjustment of their usual anti-hypertensives for the duration of bortezomib therapy.
• Thrombocytopenia: usually progressive over 21-day cycle with recovery prior to next cycle. Check FBC on D1 & D8; consider dose reduction if platelets <30 on D1 and transfuse platelets if <30 on any other treatment day.
• Fatigue

Suggested dose modifications

**Hepatic & Renal Impairment:**

**Bortezomib:**

There are no recommended dose reductions for patients with renal or hepatic impairment. The incidence of serious undesirable effects has been shown to increase in patients with mild to moderate renal impairment when compared
to patients with normal renal function. Caution should therefore be exercised when treating patients with a CrCl < 30 ml/min.

**CYCLOPHOSPHAMIDE:**

<table>
<thead>
<tr>
<th>Creatinine (mmol/L)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;300</td>
<td>100%</td>
</tr>
<tr>
<td>300-600</td>
<td>50%</td>
</tr>
<tr>
<td>&gt;600</td>
<td>omit</td>
</tr>
</tbody>
</table>

**Peripheral neuropathy:**

Patients should have a full clinical neurological assessment prior to starting bortezomib and should be monitored closely for neurological symptoms/signs at each attendance. Ensure nursing staff are educated about neuropathy and fill in the checklist before each dose. Serum B12 should be measured prior to starting treatment with Bortezomib, and all patients with B12 levels of <200 pg/ml should receive supplementation (1 mg hydroxocobalamin IM).

Cyclophosphamide rarely contributes to neuropathy. The following bortezomib dose modification schedule is recommended for the management of peripheral neuropathy:

<table>
<thead>
<tr>
<th>Severity of peripheral neuropathy</th>
<th>Modification of dose and regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (paraesthesia and/or loss of reflexes) with no pain or loss of function</td>
<td>No action</td>
</tr>
<tr>
<td>Grade 1 with pain or Grade 2 (interfering with function but not the activities of daily living)</td>
<td>Withhold bortezomib treatment until symptoms of toxicity have resolved to Grade 1. Treat with appropriate anti-neuropathic agents. When toxicity resolves re-initiate bortezomib treatment and reduce dose to 1.0 mg/m² biweekly OR change treatment schedule to 1.3 mg/m² weekly.</td>
</tr>
<tr>
<td>Grade 2 with pain or Grade 3 (interfering with activities of daily living)</td>
<td>Withhold bortezomib treatment until symptoms of toxicity have resolved to Grade 1. Treat with appropriate anti-neuropathic agents. When toxicity resolves re-initiate bortezomib treatment and reduce dose to 0.7 mg/m² biweekly OR change treatment schedule to 1 mg/m² weekly.</td>
</tr>
<tr>
<td>Grade 4 (permanent sensory loss that interferes with function)</td>
<td>Discontinue bortezomib</td>
</tr>
</tbody>
</table>

**Autonomic neuropathy, diarrhoea and hypotension:**

This can come on insidiously and careful questioning of patients for symptoms of postural dizziness and unsteadiness is essential.

<table>
<thead>
<tr>
<th>Severity of autonomic neuropathy</th>
<th>Modification of dose and regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1: Occasional dizziness on standing (&lt;3x/week)</td>
<td>No action</td>
</tr>
<tr>
<td>Grade 2: Regular dizziness on standing with no postural drop or grade 2 diarrhoea</td>
<td>Withhold bortezomib treatment until symptoms of toxicity have resolved to Grade 1. When toxicity resolves re-initiate bortezomib treatment and reduce dose to 1.0 mg/m² biweekly OR change treatment schedule to 1.3 mg/m² weekly.</td>
</tr>
<tr>
<td>Grade 3: Postural drop of ≥20 mm Hg with or without dizziness. Dizziness interfering with activities of daily living, or grade 3 diarrhoea</td>
<td>Withhold bortezomib treatment until symptoms of toxicity have resolved to Grade 1. When toxicity resolves re-initiate bortezomib treatment and reduce dose to 0.7 mg/m² biweekly OR change treatment schedule to 1 mg/m² weekly.</td>
</tr>
<tr>
<td>Grade 4: Syncopeal episodes or other autonomic disturbance e.g. &gt;grade 3 diarrhoea</td>
<td>Discontinue bortezomib</td>
</tr>
</tbody>
</table>

**Haematological toxicity:**
Neutropaenia is extremely unusual on bortezomib but may be worsened by cyclophosphamide.

Thrombocytopenia is a frequent side-effect of bortezomib. The FBC should be checked on D1 & D8. Platelet counts usually fall up to 60% from baseline with each cycle of treatment, reaching a nadir by D12. Platelet count should be >30 to treat, and patients may receive platelet transfusions to allow this. If platelet count is <30 on D1, consider dose reduction, e.g. to 1mg/m².

6.2.4 PAD

PAD (WEEKLY BORTEZOMIB)
Bortezomib 1.3mg/m²SC D1, 8, 15&22
Doxorubicin 9mg/m²/day IV bolus injections D1, 2, 3, 4
Dexamethasone 40mg orally, D1-4 (with additional pulses D8-11 & D15-18 in cycle 1)
Repeat every 28 days.

This is more myelosuppressive than BCD, so dose reductions +/- growth factors are more likely to be needed. For bortezomib-related supportive care, monitoring and dose reductions, see above appendix 6.2.3.

Doxorubicin:
Haematological toxicity:
Neutrophils must be >1.0x10⁹/l and platelets >75x10⁹/l prior to commencing treatment

Hepatic toxicity:

<table>
<thead>
<tr>
<th>Bilirubin (mmol/L)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>100%</td>
</tr>
<tr>
<td>20-51</td>
<td>50%</td>
</tr>
<tr>
<td>&gt;51</td>
<td>25%</td>
</tr>
</tbody>
</table>

6.2.5 Lenalidomide-containing regimens
Lenalidomide 25 mg daily po, D 1-21
Dexamethasone **20-40*/mg po, D1-4 (*"high-dose") (additional pulses may be given, e.g. D8-11 +/- D15-18, where rapid disease reduction is needed at start of course)
OR
Dexamethasone **20-40*/mg po weekly, D1, 8, 15 and 22 (*"low-dose") (consider in older or frailer patients)
+/-Cyclophosphamide 500mg po weekly (e.g. D1, 8, 15, 21)
Repeat every 28 days.
*40mg is the standard recommended dose, but 20mg may be used if there is a concern regarding toxicity

In responding patients, especially where steroid toxicity is an issue, dexamethasone may be given on a weekly schedule after the first 1-2 cycles, as recent evidence indicates the superiority of this regimen over pulsed dexamethasone in newly diagnosed patients (Rajkumar et al, 2009).

Supportive care:
• Stress-ulcer prophylaxis
• Aciclovir 200mg tds po
• Allopurinol 300mg od po for at least first cycle, up to cycle 3 if heavy disease burden.
• Thromboprophylaxis – see section 5.3.
• Laxatives
• Anti-emetics
Important lenalidomide toxicity
- **Cytopenias** - regular blood count monitoring is required (2-weekly for first 2 courses at least); patients may need G-CSF.
- **Venous thromboembolism** – this was significant in the US study (not in the European study), and thromboprophylaxis is recommended (see section 5.3 for risk assessment & recommendations).
- **Constipation**
- **Fatigue**
- **Neuropathy**: less frequent than with thalidomide or bortezomib but those with pre-existing neuropathy may develop worsening symptoms.

Suggested lenalidomide dose modifications

**Haematological toxicity:**
A FBC should be performed at baseline, fortnightly for the first 2 months of treatment and at least monthly thereafter. Dose adjustments are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia (or any other grade 3 or 4 toxicity attributed to lenalidomide).

The following recommendations are based upon the SPC; however an alternate dosing strategy may be considered (Popat et al., BJH 2015)

<table>
<thead>
<tr>
<th>Starting daily dose</th>
<th>25mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose level – 1</td>
<td>15mg</td>
</tr>
<tr>
<td>Daily dose level – 2</td>
<td>10mg</td>
</tr>
<tr>
<td>Daily dose level – 3</td>
<td>5mg</td>
</tr>
</tbody>
</table>

**Thrombocytopenia**
During phase III studies, grade 3 or 4 thrombocytopenia occurred in over 10% of patients who received lenalidomide and dexamethasone. The incidence was higher in patients with impaired renal function, occurring in 18.8% of patients with CrCl <30ml/min but only 4.6% in patients with CrCl >50ml/min.

<table>
<thead>
<tr>
<th>Platelet count</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>When platelets first fall to &lt;30x10^9/L</td>
<td>Pause lenalidomide treatment</td>
</tr>
<tr>
<td>Return to &gt;30x10^9/L</td>
<td>Resume at dose level – 1</td>
</tr>
<tr>
<td>For each subsequent drop to &lt;30x10^9/L</td>
<td>Pause lenalidomide treatment</td>
</tr>
<tr>
<td>Return to &gt;30x10^9/L</td>
<td>Resume at next lower dose level; do not dose below 5mg daily.</td>
</tr>
</tbody>
</table>

**Neutropenia**
Grade 3-4 neutropenia occurs in around 30% of patients who receive the combination of lenalidomide and dexamethasone.

<table>
<thead>
<tr>
<th>Neutrophil count</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>When neutrophils first fall to &lt;0.5x10^9/L</td>
<td>Pause lenalidomide treatment</td>
</tr>
<tr>
<td>Return to &gt;0.5x10^9/L (and neutropenia is the ONLY toxicity)</td>
<td>Resume at starting dose</td>
</tr>
<tr>
<td>Return to &gt;0.5x10^9/L (with other dose-dependent haematological toxicity present)</td>
<td>Resume at dose level – 1</td>
</tr>
<tr>
<td>For each subsequent drop to &lt;0.5x10^9/L</td>
<td>Pause lenalidomide treatment</td>
</tr>
<tr>
<td>Return to &gt;0.5x10^9/L</td>
<td>Resume at next lower dose level; do not dose below 5mg daily.</td>
</tr>
</tbody>
</table>
**Renal or hepatic impairment:**
There are currently no recommendations for dose adjustments for patients with renal or hepatic insufficiency. Given the increased incidence of grades 3 and 4 thrombocytopenia in patients with impaired renal function, careful platelet monitoring is highly recommended in patients with elevated serum creatinine.

### 6.2.6 MPT

Melphalan 0.25mg/kg* po once daily, D1-4; NB. Melphalan tablets are only available in a 2mg strength.
Prednisolone 2mg/kg po once daily, D1-4
Thalidomide up to 200 mg (as tolerated) po once daily continuously (D1-28)
*Repeat every 28 days.*

**Supportive care:**
- Stress-ulcer prophylaxis
- Aciclovir 200mg tds po
- Allopurinol 300mg od po for at least first cycle, up to cycle 3 if heavy disease burden.
- Thromboprophylaxis – see section 5.3
- Laxatives
- Anti-emetics

For further information regarding thalidomide prescribing and dose modification see appendix 6.2.2.

**Suggested dose modifications**

Melphalan:
*Consider reducing dose to 0.2mg/kg po once daily D1-4 in those >75 years.*

**Haematological toxicity:**
Neutrophils must be >1.3x10⁹/l and platelets >75x10⁹/l prior to commencing treatment (patients with cytopenias should be treated on the CTDa protocol).

**Renal impairment:**
In patients with moderate to severe renal impairment currently available pharmacokinetic data do not justify an absolute recommendation on dosage reduction; it may be prudent to use a reduced dose initially and monitor closely for myelosuppression.

### 6.2.7 MPV

Melphalan 9 mg/m² po once daily, D1-4
Prednisolone 60mg/m² po once daily, D1-4
Bortezomib 1.3 mg/m D 1, 8, 15 & 22 by sc injection
*Repeat every 6 weeks.*

**Supportive care:**
- Stress-ulcer prophylaxis
- Aciclovir 200mg tds po
- Allopurinol 300mg od po for at least first cycle, up to cycle 3 if heavy disease burden.
- Laxatives
- Anti-emetics

**Suggested dose modifications:**
See appendix 6.2.3 for modifications to bortezomib.

### 6.2.8 Cyclophosphamide priming
PLEASE CHECK LOCAL PROTOCOL

Cyclophosphamide 1500mg/m\(^2\) IV infusion in 0.9% Saline over 2 hours at t=0, day 1
Mesna 300mg/m\(^2\) IV bolus at t=0, day 1
Mesna 600mg/m\(^2\) po at t=+2h and t=+6h, day +1
GCSF SC daily (at a dose of 5mcg/kg/day), from day +2 until harvesting completed

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Patient weight</th>
<th>Daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenograstim</td>
<td>&lt; 85kg</td>
<td>263mcg SC</td>
</tr>
<tr>
<td></td>
<td>&gt; 85kg</td>
<td>526mcg SC</td>
</tr>
<tr>
<td>OR</td>
<td>&lt;48kg</td>
<td>5mcg/kg SC</td>
</tr>
<tr>
<td></td>
<td>48-60kg</td>
<td>300mcg SC</td>
</tr>
<tr>
<td></td>
<td>61-96kg</td>
<td>480mcg SC</td>
</tr>
<tr>
<td></td>
<td>&gt;96kg</td>
<td>780mcg SC</td>
</tr>
</tbody>
</table>

Supportive care
- Mesna - available as 400mg and 600mg tablets (round up the dose to the nearest whole tablet).
- Anti-emetics
- Stress-ulcer prophylaxis

Advice to the patient
Patient should be given written information on oral mesna tablets and be counseled on the following points:
- To consume 2-3L of fluid for the remainder of day 1 and again on day 2
- Timing of mesna tablet administration
- To monitor for haematuria, pain on micturition and to contact the ward if these symptoms appear
- To contact the ward if patient experiences uncontrolled nausea and vomiting or frank haematuria

Suggested dose modifications

Renal Impairment:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>100%</td>
</tr>
<tr>
<td>10-50</td>
<td>75%</td>
</tr>
<tr>
<td>&lt;10</td>
<td>50%</td>
</tr>
</tbody>
</table>

In patients with any reduction in renal function (GFR < 50 ml/min), consider priming using IV cyclophosphamide, IV mesna and 24hrs of IV fluids (requiring overnight stay). Patients receiving haemodialysis should be dialysed 14 hours post completion of cyclophosphamide administration (Perry, et al 1999).

Hepatic Impairment:
No dose adjustment necessary.

6.2.9 ESHAP priming

Etoposide 40mg/m\(^2\) IV once daily in 250ml N/Saline over 1 hour, D1-4
Methyprednisolone 500mg IV once daily in 100ml N/Saline over 30 mins, D1-5
Cytarabine 2000mg/m\(^2\) IV single dose in 500ml N/Saline over 3 hours, D1
Cisplatin 25mg/m\(^2\) continuous IV infusion in 1000ml N/Saline (or via CADD pump), D1-4 (total dose 100mg/m\(^2\))

These patients generally need indwelling central access (PICC or Hickman lines). For patients having stem cell harvest: Start GCSF on Day +6 until completion of HPC-A (haemopoietic progenitor cells – apheresis) collection (dosing as per cyclophosphamide priming).
Hydration (D1-4)
Sodium Chloride 0.9% 1000ml +20mmol KCL +10g mannitol over 24 hours OR
Sodium Chloride 0.9% 1000ml +20mmol KCL +10g mannitol over 12 hours x 2 in patients receiving cisplatin via a CADD pump.

Monitor patient closely for signs of fluid overload; this should be managed conservatively (i.e. reduce hydration fluid volume). If patient has inadequate urine output, consider mannitol (e.g. 200mls 10% mannitol intravenously over 30 minutes). Frusemide should be used with caution.

The ESHAP regimen may be administered in the ambulatory care setting if the patient is capable of sufficient oral fluid intake.

Supportive care
• Stress-ulcer prophylaxis
• Aciclovir 200mg tds po
• Co-trimoxazole 960mg od Mon/Wed/Fri po
• Anti-emetics – as per local policy – this may be a very emetogenic regimen
• Prednisolone 0.5% eye drops: 1drop per eye qds D1-8 (to prevent cytarabine-induced conjunctivitis)

Suggested dose modifications
Minimum Haematological counts before initiating therapy:
Neutrophils >1x10^9/l
Platelets >75x10^9/l

Renal Impairment:
Cisplatin:

<table>
<thead>
<tr>
<th>GFR (ml/min)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60</td>
<td>100%</td>
</tr>
<tr>
<td>50-60</td>
<td>75%</td>
</tr>
<tr>
<td>40-50</td>
<td>50%</td>
</tr>
<tr>
<td>&lt;40</td>
<td>Omit – consider carboplatin</td>
</tr>
</tbody>
</table>

Cytarabine:

<table>
<thead>
<tr>
<th>GFR (ml/min)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60</td>
<td>100%</td>
</tr>
<tr>
<td>45-60</td>
<td>60%</td>
</tr>
<tr>
<td>30-45</td>
<td>50%</td>
</tr>
<tr>
<td>&lt;30</td>
<td>Omit</td>
</tr>
</tbody>
</table>

Etoposide:

<table>
<thead>
<tr>
<th>GFR (ml/min)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60</td>
<td>100%</td>
</tr>
<tr>
<td>45-60</td>
<td>85%</td>
</tr>
<tr>
<td>30-45</td>
<td>80%</td>
</tr>
<tr>
<td>15-30</td>
<td>75%</td>
</tr>
<tr>
<td>&lt;15</td>
<td>50%</td>
</tr>
</tbody>
</table>

Hepatic Impairment:
The need for dose reduction of etoposide and cytarabine in liver impairment is controversial.

Etoposide:

<table>
<thead>
<tr>
<th>Bilirubin (mmol/L)</th>
<th>AST (U/L)</th>
<th>Dose</th>
</tr>
</thead>
</table>
Cytarabine:

<table>
<thead>
<tr>
<th>Bilirubin (mmol/L)</th>
<th>AST (U/L)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;34</td>
<td>Or</td>
<td>&gt;180</td>
</tr>
</tbody>
</table>

Neurotoxicity:
Cytarabine should be stopped immediately if neurotoxicity occurs during administration.
6.3 Current trials open

Please refer to the following website:

6.4 Serum free light chain assay: indications for use & interpretation

Free light chains are incorporated into immunoglobulins (Igs) during B cell development, and continue to be produced throughout the rest of B cell maturation up to the plasma cell stage, when secretion is at its highest level. Both normal and neoplastic plasma cells secrete FLC as well as whole immunoglobulin. An abnormal κ:λ ratio supports the presence of clonal plasma cell expansion, with false positive results ranging between 0 and 4% (generally κ-biased ratios attributed to polyclonal plasmacellular expansion or renal impairment). Quantification of free κ and λ concentrations is performed on automated nephelometric or turbidimetric platforms and normal reference ranges have been defined in the general population:

K 3.3- 19.4 mg/l
λ 5.7- 26.3 mg/l
Ratio: 0.26- 1.65 (100% range); NB. The FLC ratio needs interpretation with great caution and is not interpretable when either the kappa or lambda values are less than 10mg/l.

6.4.1 Normal

In normal individuals, approximately 0.5-1 g/day of FLC are produced by BM and LN cells; these molecules enter the blood stream and are partitioned into the intravascular and extravascular compartments. There is approximately a 40% FLC production in excess of heavy chains to allow proper conformation of intact immunoglobulins. Under normal circumstances, FLC are filtered through glomerular pores at a rate that is dependent on their size.

 Serum κ light chains (monomeric) are cleared in 2-4 hours, while λ light chains (typically dimeric) are cleared in 3-6 hours. Although there are twice as many κ- than λ-producing plasma cells, since κ light chains filter 3 times as fast as λ, normal serum concentrations of λ exceed those of κ under normal circumstances.

Normally functioning kidneys can reabsorb between 10-30 g/day of FLC, so very little FLC typically passes beyond the proximal tubules. In the distal urinary tract, a small amount of FLC (1-10 mg/day) is secreted by mucosal cells, so normal urine contains a small amount of FLC as well as secretory IgA.

6.4.2 Renal impairment

When renal impairment develops and glomerular function declines, fewer FLCs are filtered, resulting in a steep rise in SFLC and a decline in urinary light chain concentration. This may be of particular importance in BJ-only myeloma in which reliance has traditionally been placed on 24 hour urine BJF quantification.

A ‘renal range’ for the ratio (0.30-3.1) has been proposed (but not yet validated), to be used in people with renal impairment (GFR<30ml/min), to take account of the alteration in FLC handling under this circumstance.

When renal clearance of FLCs falls, removal by other tissues rises (by pinocytosis of serum), hence there is no distinction between κ and λ removal rates. However, serum κ levels rise preferentially as their normally greater renal removal is reduced by the renal impairment. Thus the κ:λ ratio rises in renal failure.

6.4.3 Clinical pitfalls

Abnormal SFLC ratios also occur when there is dysregulation of immunoglobulin production, e.g. in SLE or HIV infection, and during immune reconstitution following stem cell transplantation. It should also be noted that polyclonal FLC may be detected in urine when their production is greatly increased (usually in association with hypergammaglobulinaemia) and/or renal reabsorption is reduced by renal tubular damage, e.g. in SLE. Polyclonal FLC in urine are not indicative of a plasma cell dyscrasia.

6.4.4 The serum free light chain assay

Typical sensitivity levels of the various techniques for detecting monoclonal proteins are:
- Serum electrophoresis 1-2 g/l
• Immunofixation 0.15-0.5 g/l
• SFLC assay <0.001 g/l

The assay is based on a commercial reagent comprising a set of polyclonal antibodies that react with epitopes on light chains that are hidden when bound to heavy chains, but become available when unbound. It is performed by immunonephelometry and can be performed on a number of automated instruments. The assay measures κ FLC and λ FLC.

Normal ranges were defined by analysing frozen sera from 182 healthy donors. The 95% reference interval for κ FLC was 3.3–19.4 mg/L, and that for λ FLC was 5.7–26.3 mg/L. For the κ/λ ratio, the 95% reference interval was 0.3–1.2, but it was decided that diagnostic range should include 100% of donors, making the normal diagnostic range for FLC κ/λ (FLCr) 0.26–1.65. Using the 100% confidence interval increased the specificity of the test from 95% to 100%, with a drop in sensitivity from 98% to 97%.

Patients with ratios greater than 1.65 contain excess κ FLC and are presumed to be producing clonal κ FLC. Patients with ratios less than 0.26 contain excess λ FLC and are presumed to be producing clonal λ FLC.

The 100% confidence interval used reduces the likelihood that polyclonal activation of B cells will cause an abnormal ratio. However, this is possible, and therefore the test must be interpreted in the context of the clinical situation. If a patient is in the midst of an infection or a flare of a rheumatological condition, the test should be repeated at a later date.

There are prevailing concerns relating to lot-to-lot variation between batches of antisera, non-linear dilution of some monoclonal FLC and falsely low results with nephelometric techniques in the presence of antigen excess, among others.


SCREENING FOR A PLASMA CELL DISORDER:
“The SFLC assay in combination with SEP and IF (in the absence of urine EP) is sufficient to screen for a pathological plasma cell disorder, other than AL amyloidosis, which requires all the serum tests as well as 24-hour urine EP”. There may be a small percentage of AL amyloid patients whose FLC production is very low (100-200mg/l) and due to the extent of renal damage in AL amyloid patients the FLC may leak through the glomeruli and into the urine, causing the potential to fail detection using SLFC assay without urine EP.

“If any diagnosis of a plasma cell disorder is made, then 24 hour urine EP and IF should be carried out”.

PROGNOSTIC VALUE OF THE SFLC ASSAY:

• MGUS: The third of MGUS patients who have an abnormal FLCr have a higher rate of progression than those who do not. A risk model based on abnormal FLCr, PP>15g/l, non-IgG isotype demonstrated a risk of progression at 20 years of 5%, 21%, 37% or 58% for 0, 1, 2 or 3 risk factors respectively.

• Asymptomatic myeloma: Abnormal FLCr predicts for a higher rate of progression. A risk model has been constructed based on abnormal FLCr, BMPC >/= 10% and PP >/= 30g/l: patients with 1, 2 or 3 risk factors had 5 year progression rates of 25%, 51% and 76% respectively.

• Solitary plasmacytoma: Up to 75% of SPB patients have an M protein in blood (usually <10g/l) or urine. Despite treatment, approximately 50% of patients develop myeloma at a median of 21 months. Persistence of an M-band for >1 year after radiotherapy has been recorded as an adverse prognostic factor for the development of myeloma. Abnormal FLCr at diagnosis is associated with a higher risk of progression to myeloma (44% compared to 26% at 5 years). One to 2 years following diagnosis, a persistent PP of 0.5g/l or greater was an additional risk factor for progression. A risk model has been constructed based on normal or abnormal FLCr, and PP>0.5g/l. Low, intermediate and high risk groups had 5 year progression rates of 13%, 26% and 62% respectively (p<0.001)

• Myeloma: Approximately 95% of newly diagnosed myeloma patients have an abnormal FLCr. Thus an abnormal FLCr in itself is not an independent adverse prognostic factor. However, greater deviation from the normal range does demonstrate prognostic significance (e.g those patients whose ratio was outside 0.25 - 4.0 or 0.125 - 8.0). Several studies have shown that baseline SFLC abnormalities are prognostic for survival in myeloma patients. When abnormal FLCr (selected cut-off points <0.03 or >32) is added to the ISS, stage 3 patients have a 5 year disease-specific survival of 16% if the FLCr is abnormal compared to 52% if it is normal.
• **AL amyloidosis**: In a cohort of 113 patients with AL amyloidosis undergoing ASCT, there was a significantly higher risk of death in patients with a higher baseline FLC (hazard ratio 2.6, p<0.4). Baseline FLC correlated with higher serum cardiac troponin levels and greater organ involvement.

“**SFLC assay should be measured at diagnosis in all patients with MGUS, asymptomatic or active myeloma, solitary plasmacytoma and AL amyloidosis**”.

**RESPONSE ASSESSMENT:**

Although FLC response can be considered for use in 3 contexts (oligosecretory (<10g/l) disease, BJ-only myeloma and myeloma with a measurable intact immunoglobulin), routine use of the assay is only recommended for oligosecretory disease and for documenting stringent CR. Few studies to date validate the usefulness of serial FLC measurements in other situations.

In oligosecretory disease (including AL amyloidosis and oligosecretory myeloma), the evidence linking changes in SLFC measurements to overall survival is restricted to **AL amyloidosis**. Studies from the major AL amyloidosis groups have demonstrated that patients who achieve a >50% reduction in their involved FLC (iFLC) are more likely to live longer (Lachmann et al) or have a trend towards improvement in haematological and organ response (Dispenzieri et al; Sanchorawala et al; Palladini et al).

In **oligosecretory MM**, there are no data to verify that FLC changes correlate with BM plasmacytosis or overall disease status, but the assumption has been made that this is the case, based on anecdotal information. Two-thirds of non-secretory (by conventional criteria) patients demonstrate abnormal iFLC and FLCr. A minimum of 100mg/l of involved FLC is required in order to use SFLC analysis in the serial follow up of oligosecretory patients.

Although the SLFC assay has excellent sensitivity in detecting FLC in patients with BJ-only MM, there is not a strong correlation between serum FLC and urine light chain load by urine EP over time.

Monitoring SLFC in **MM patients with a measurable PP** is only recommended under the following circumstances:

1. SFLC levels may be more sensitive for the early detection of lack of response and early detection of relapse than standard tools, but no one has shown that this kind of information ultimately affects patient outcome.
2. To define stringent CR: now included in the IMWG Uniform Response Criteria.
3. To detect light chain escape in patients with advanced disease. In late stage disease, a subclone of malignant plasma cells may expand, that is incapable of producing significant amounts of Ig heavy chains, but retains the ability to maintain light chain production. Unless urine EP is done periodically, this phenomenon (which may increase the risk of renal impairment) may be missed.

In the follow up of treated disease, either the involved FLC or the difference between involved and uninvolved FLC should be used (dFLC). The ratio is not useful because significant immunosuppression of the uninvolved FLC occurs during chemotherapy and this can induce extreme ratios that do not reflect changes in tumour load.

Thus the IMWG recommends that:

“**Serial FLC should be routinely performed in all patients with AL amyloidosis and oligosecretory MM. It should also be done in all patients who achieve CR to determine whether they have attained stringent CR**”.

Although not yet validated, the IMWG has published updated response criteria, which incorporate the SFLC assay (see below).
<table>
<thead>
<tr>
<th>Condition</th>
<th>Minimum to be deemed measurable</th>
<th>PR</th>
<th>CR</th>
<th>sCR</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL&lt;sup&gt;1&lt;/sup&gt; without measurable&lt;sup&gt;1&lt;/sup&gt;</td>
<td>dFLC ≥ 100 mg/L</td>
<td>50% reduction of dFLC</td>
<td>Normal ifLC &amp; CR by IFE &amp; bone marrow</td>
<td>ND</td>
<td>50% increase of dFLC to &gt; 100 mg/L</td>
</tr>
<tr>
<td>serum or urine M protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AL&lt;sup&gt;1&lt;/sup&gt; with measurable&lt;sup&gt;1&lt;/sup&gt;</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>serum or urine M protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MM&lt;sup&gt;1&lt;/sup&gt; without measurable&lt;sup&gt;1&lt;/sup&gt;</td>
<td>dFLC ≥ 100 mg/L and ifLC abnormal</td>
<td>50% reduction of dFLC</td>
<td>ND</td>
<td>Normal ifLC &amp; CR by IFE &amp; bone marrow</td>
<td>50% increase of dFLC</td>
</tr>
<tr>
<td>serum or urine M protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MM with measurable disease&lt;sup&gt;2,3&lt;/sup&gt;</td>
<td>Use of FLC not recommended</td>
<td>Use of FLC not recommended</td>
<td>Use of FLC not recommended</td>
<td>Normal ifLC &amp; CR by IFE &amp; bone marrow</td>
<td>Use of FLC not recommended</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

iFLC, involved free light chain, i.e. κ for a patient with κ restricted disease and λ for a patient with λ restricted disease; dFLC, difference between iFLC and uninvolved FLC; ND, not defined

<sup>1</sup> Measurable M protein includes serum M-protein of at least 1 g/dL or a urine M-protein of at least 200 mg/24 hours for myeloma patients (100 mg/24 hours for AL patients).
6.5 Suggested Myeloma Venous thromboembolism (VTE) Risk Assessment Proforma

This should be carried out
- At diagnosis
- At the start of any new treatment regimen
- At relapse
- On admission electively or for emergency care

### STEP ONE: REVIEW THROMBOSIS RISK FACTORS and tick each box that applies – any tick should prompt consideration of pharmacological prophylaxis with aspirin, dalteparin or warfarin.

**Individual risk factors**
- Personal or family history of VTE
- Acute medical illness e.g. infection, acute renal failure, vomiting or dehydration
- Co-morbidities: cardiac, diabetes, chronic renal impairment, chronic inflammatory disease
- Obesity (BMI ≥ 30)
- Immobility (acute or chronic)
- Thrombophilias, myeloproliferative disorders, haemoglobinopathies
- Recent surgery (within 6 weeks): neuro-, trauma, orthopaedic, general, any other anaesthesia
- Medications: erythropoiesis stimulating agents, HRT, tamoxifen/stilboestrol

**Myeloma-risk factors**
- At diagnosis
- Hyperviscosity

**Myeloma therapy**
- Lenalidomide or thalidomide
- Doxorubicin
- High-dose steroid (≥ 480mg/month dexamethasone or equivalent)
- Combination chemotherapy

### STEP TWO: if none of the boxes from Step One is ticked, the patient is at low risk of VTE and no intervention is required.

**Patient at low risk of VTE**

### STEP THREE: REVIEW BLEEDING RISK FACTORS and tick each box that applies – any tick should prompt clinicians to consider if bleeding risk is sufficient to preclude pharmacological prophylaxis.

- Active bleeding
- Haemophilia or other known bleeding disorder
- Platelet count <100 x10^9/l
- Acute stroke in previous month (haemorrhagic or ischaemic)
- Blood pressure >200mmHg systolic or >120mmHg diastolic
- Severe liver disease (abnormal PT or known varices)
- Severe renal disease (CrCl <30ml/min)
- Undergoing procedure or intervention with high bleeding risk

### STEP FOUR: if thromboprophylaxis is indicated, review if there ANY SPECIFIC CONTRAINDICATIONS OR CAUTIONS TO ASPIRIN OR DALTEPARIN use.

- Hypersensitivity to heparin/ LMWH/ aspirin or history of HIT
- Bacterial endocarditis / pericarditis (liaise with Cardiology)
- Current or recent history of peptic ulcer disease

### STEP FIVE: SELECT APPROPRIATE THROMBOPROPHYLAXIS if required – tick chosen strategy.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose and Administration</th>
<th>Conditions for Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin 75mg od. PO</td>
<td>Only for those on lenalidomide with ≤ 1 additional risk factors</td>
<td></td>
</tr>
<tr>
<td>Dalteparin 5000units od. SC</td>
<td>For those with 1 to 2 additional risk factors</td>
<td></td>
</tr>
<tr>
<td>Dalteparin 200units/kg od. SC (24hr max 18,000 units)</td>
<td>For those with 3 additional risk factors</td>
<td></td>
</tr>
</tbody>
</table>

- Is the weight <45kg or BMI >40; or CrCl <30ml/min? (consider dose reduction )
- Are there any bleeding risk factors? (divide dose)
- Is weight >100kg (seek advice re dosing)
- Is CrCl less than 30ml/min? Treatment dose dalteparin should generally be
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<table>
<thead>
<tr>
<th>Warfarin (target INR 2.5)</th>
<th>avoided – seek haemostasis advice.</th>
</tr>
</thead>
<tbody>
<tr>
<td>For those with 3 additional risk factors</td>
<td></td>
</tr>
</tbody>
</table>
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