

Guidelines for the management of Multiple Myeloma

These guidelines should be read in conjunction with the latest National Cancer Drug Fund information, NICE guidance and published BCSH guidelines.

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Written July 2019

Review July 2021

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1. Introduction

Myeloma has a UK age-standardised incidence of 5.4 per 100,000. There are approximately 5,500 new cases diagnosed each year in the UK. The median age at presentation is 70 years with <2% presenting under 40 years. It is more common in men and Afro-Caribbean's.¹

2. Diagnosis and staging

Presenting features are varied and usually reflect end organ dysfunction in the form of anaemia, bone pain and/or pathological fractures, fatigue, increased infections, renal failure and hypercalcaemia.

Although most patients are diagnosed with myeloma, some patients with myeloma may also produce amyloid (approximately 10%) and some do not have myeloma but systemic AL Amyloidosis. Watch out for signs and symptoms of AL Amyloidosis such as severe fatigue, nephrotic syndrome with ankle swelling, shortness of breath, symptoms consistent with carpal tunnel syndrome, diarrhoea (possibly with blood) or constipation, an enlarged tongue, difficulty swallowing, easy bruising, unusual rash, purplish patches around the eyes or cardiac arrhythmias. Management hinges on prompt diagnosis and recognition of complications, many of which are at least partially reversible.

2.1 Baseline Investigations²⁻³

2.1.1 Bloods:

- FBC, clotting screen (PT, APTT, TT, fibrinogen)
- U&Es, LFTs, bone profile (corrected calcium, phosphate), eGFR
- LDH, Urate, CRP
- Serum protein electrophoresis with immunofixation and paraprotein (PP) quantification
- Serum Free Light Chain (SFLC) assay
- NT-proBNP and Troponin if suspected cardiac amyloid

2.1.2 Urine:

- Spot urine for Bence Jones protein (BJP); not quantitative but can be used for monitoring
- Consider 24hr urinary protein excretion with protein electrophoresis, immunofixation and quantification of BJP. If concerns regarding inaccurate collection, Urine Protein/Creatinine ratio can be assessed

2.1.3 Bone marrow (BM):

- BM aspirate & trephine plus

- FISH for t(4;14), t(14;16), del(17p) and 1p-/1q+ on purified plasma cells (PCs)
- Informative flow cytometry markers are combined CD38, CD138 and CD45 for identification and CD19, CD56, CD27, CD81, CD117 for further characterization of BM PCs (optional); useful minimal residual disease (MRD)

2.1.4 Radiology as per NICE guidance:⁴

- Newly diagnosed myeloma patients, in order of preference:
 - MRI, whole-body
 - CT, whole-body low-dose
 - Skeletal survey is allowed only if the above-mentioned tests are not possible for medical reasons or declined by patient
- PET-CT is recommended for soft tissue plasmacytomas
- MRI of spine in suspected spinal cord compression
- Symptom-directed imaging if new bone symptoms develop

2.1.5 Cardiology:

- ECG
- Echo or MUGA if suspected cardiac amyloid
- Cardiac MR and DPD scintigraphy if cardiac amyloid is suspected

2.2 Diagnostic Criteria⁵⁻⁶

2.2.1 Symptomatic multiple myeloma

- Monoclonal plasma cells in BM $\geq 10\%$
- Serum paraprotein $\geq 30\text{g/L}$ (if IgM PP exclude lymphoplasmacytic lymphoma)

Myeloma-related end organ damage or tissue injury (ROTI) and commonly called the CRAB criteria:

C: Hypercalcaemia (corrected $\text{Ca}^{2+} > 2.75\text{mmol/L}$)

R: Renal impairment (no other cause) – $\text{CrCl} < 40$, $\text{Cr} > 177$

A: Anaemia (Hb $< 100\text{g/L}$ or $< 20\text{g}$ below normal) not due to other causes

B: Bone lesions (lytic lesions or osteoporosis)

International Myeloma Working Group (IMWG) guidance recommends treatment of myeloma patients without CRAB features but one of the following:

- Bone marrow plasma cell percentage $\geq 60\%$
- SFLC ratio ≥ 100
- More than one focal bone lesion $> 0.5\text{ cm}$ on MRI studies

These criteria were found to be associated with at least an 80% risk of progression from asymptomatic to symptomatic myeloma within 2 years. They offer the option to treat patients with significant tumour burden at an earlier time point to avoid risk of irreversible end organ damage. However, as there is lack of evidence that early treatment makes a difference to outcome and prospective data collection is required, we recommend individual case discussion at MDT.

2.2.2 Smouldering asymptomatic multiple myeloma

- Monoclonal serum protein $\geq 30\text{g/L}$ and/or BJP $\geq 500\text{mg/24hr}$
- Monoclonal plasma cells in BM $\geq 10\%$
- Absence of CRAB or IMWG criteria

2.2.3 Monoclonal gammopathy of undetermined significance (MGUS)

- Monoclonal serum protein $< 30\text{g/L}$ and/or BJP $< 500\text{mg/24hr}$
- Monoclonal plasma cells in BM $< 10\%$
- Absence of CRAB or IMWG criteria
- Absence of other B cell proliferative disorder or amyloid

2.2.4 Solitary plasmacytoma of bone

- Single lytic bony lesion composed of clonal plasma cells on biopsy
- Monoclonal serum protein $< 30\text{g/L}$ and/or BJP $< 500\text{mg/24hr}$
- Monoclonal plasma cells in BM $< 10\%$
- Absence of CRAB or IMWG criteria
- Absence of other B cell proliferative disorder or amyloid

2.2.5 Extramedullary plasmacytoma⁷

- Soft tissue mass composed of clonal plasma cells on biopsy
- Monoclonal serum protein $< 30\text{g/L}$ and/or BJP $< 500\text{mg/24hr}$
- Monoclonal plasma cells in BM $< 10\%$
- Absence of CRAB or IMWG criteria
- Absence of other B cell proliferative disorder or amyloid

2.2.6 Monoclonal deposition disease (AL Amyloidosis, light chain deposition)⁸

- Biopsy-proven interstitial protein deposition (typing of amyloid is mandatory)
- Presence or absence of monoclonal serum or urine protein
- Monoclonal plasma cells in BM $< 10\%$

If AL Amyloid is present it is important to distinguish whether patients also have multiple myeloma; if present patients should be treated as per myeloma pathway.

2.2.7 POEMS syndrome⁹

This requires the presence of both mandatory criteria with one other major criterion and one other minor criterion.

Mandatory criteria

- Monoclonal plasma cell disorder (e.g. serum PP, usually λ light chain)
- Peripheral neuropathy

Major criteria

- Castleman's disease
- Osteosclerotic bone lesions
- Elevated vascular endothelial growth factor (VEGF)

Minor criteria

- Organomegaly
- Oedema
- Endocrine disorder (excluding DM and hypothyroidism)
- Skin changes
- Papilloedema
- Thrombocytosis / polycythaemia

2.3 Staging and Risk Stratification

The International Staging System (ISS) has now replaced the Durie-Salmon staging system.¹⁰ The R-ISS staging system is a new risk stratification algorithm with an improved prognostic power incorporating ISS, chromosomal abnormalities (CA), and LDH levels.¹¹

Table 1: Revised ISS

Table 1. Standard Risk Factors for MM and the R-ISS	
Prognostic Factor	Criteria
ISS stage	
I	Serum β_2 -microglobulin < 3.5 mg/L, serum albumin \geq 3.5 g/dL
II	Not ISS stage I or III
III	Serum β_2 -microglobulin \geq 5.5 mg/L
CA by iFISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	No high-risk CA
LDH	
Normal	Serum LDH < the upper limit of normal
High	Serum LDH > the upper limit of normal
A new model for risk stratification for MM	
R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH

Abbreviations: CA, chromosomal abnormalities; iFISH, interphase fluorescent in situ hybridization; ISS, International Staging System; LDH, lactate dehydrogenase; MM, multiple myeloma; R-ISS, revised International Staging System.

Table 2: International Staging System (ISS)

Stage	Criteria
I	Serum β 2M <3.5mg/L and albumin \geq 35g/L
II	Neither I or III
III	Serum β 2M >5.5mg/L

3. Treatment of Myeloma and Related Disorders

Treatment should be started as soon as possible with the aim to prevent end organ damage. Good supportive care, including bisphosphonates unless medically contraindicated (i.e. dental extraction needed, poor renal function) are also key.

ALLWAYS CONSIDER CLINICAL TRIALS FIRST; in the absence of a suitable clinical trial consider (see appendix for details of chemotherapy regimens):

3.1 Young and fit patients: First line

3.1.1 Velcade containing regimens

- VTD (Velcade, Thalidomide, Dexamethasone)¹³
- VCD (Velcade, Cyclophosphamide, Dexamethasone)¹⁴
- VD (Velcade, Dexamethasone)

Bortezomib is given SC bi- or once weekly with oral hydration (3L/day) plus acyclovir prophylaxis. In patients with severe skin reactions in the site of injection or patients with severe fluid overload, IV Velcade may be considered.

VGPR and PR rates were significantly higher with VTD when compared to VCD prior to ASCT.¹⁶ In a Phase 3 randomised trial comparing VCD vs PAD, VCD was found to be as effective as PAD in all myelomas as well as in those with renal impairment.¹⁸ Therefore, due to its IV administration and cumulative cardiotoxicity PAD as induction treatment is not anymore recommended.

3.1.2 Thalidomide containing regimens

For some patients oral regimens may be preferable. Although no head-to-head trials are available comparing bortezomib- and thalidomide-based regimens, it is largely accepted that the former induces deeper responses and longer remissions.

- CTD (Cyclophosphamide, Thalidomide, Dexamethasone)¹⁸
- CTDa (Cyclophosphamide, Thalidomide, attenuated Dexamethasone)

3.1.3 High dose therapy (HDT) and stem cell rescue

High dose melphalan and autologous stem cell transplantation (ASCT) are considered standard of care in first and second (and occasionally third) remission if

patients are deemed fit. Broadly, those ≤ 70 years and at times up to 75 years (if no comorbidities) are considered fit for HDM and ASCT.

Fitness is assessed on performance score, tolerance of induction treatment and comorbidities (in particular renal, cardiac and pulmonary function). If transplant-eligible the use of bortezomib-based treatment has been shown to be superior to that with thalidomide.¹⁹ Induction regimens containing Melphalan are to be avoided in order to preserve stem cell mobilisation.

Stem cell mobilisation can be obtained using Cyclophosphamide 1.5 or 2g/m² followed by G-CSF 5-10 μ g/kg from the day after Cyclophosphamide administration, with mobilisation expected around day +8-10. Alternatively, G-CSF at 16 μ g/kg can be used, with cells harvested on the 5th and 6th day of administration.

The aim should be to collect $>4 \times 10^6$ /kg CD34⁺ sufficient for two ASCTs. In patients above the age of 70 the aim of collection could be reduced to $>2 \times 10^6$ /kg CD34⁺ and similarly in patients below the age of 50 a collection of $>6 \times 10^6$ /kg CD34⁺ should be considered.

In 10-15% the addition of Plerixafor (CXCR4 antagonist) is required to perform a successful stem cell collection. Plerixafor can be used pre-emptively in patients with poor mobilisation characterised by low circulating CD34 counts at time of collection. Importantly, only 3 doses of Plerixafor are allowed per patient according to the current rules. For details please follow NHS England's commissioning document.

HDM and ASCT is also feasible for patients with severe renal failure and those on dialysis, but the decision should be carefully evaluated due to the increased risk of transplant related toxicity including transplant related mortality (TRM).

3.1.4 Maintenance treatment following HDT

Although several phase 3 studies have been published recently demonstrating clinical benefit of maintenance therapy, no strategy has so far been adopted as the standard of care in this setting.

3.1.5 Allogeneic stem cell transplant

The allogeneic stem cell transplant (AlloSCT) could be an option in a small subgroup of patients such as young and fit patients with high-risk disease (e.g. TP53 deletion, rapid relapse following induction therapy) and hence characterised by poor outcome following standard treatment or even ASCT.

3.2 Older patients not fit for HDT: First line

Where possible patients should be offered entry into a clinical trial. If a patient does not wish to enrol in a clinical trial, the following treatments can be considered.

3.2.1 Velcade containing regimens

- VCD (Velcade, Cyclophosphamide, Dexamethasone)¹⁴

- VD (Velcade, Dexamethasone)
- VMP (Velcade, Melphalan, Dexamethasone)¹⁵

3.2.2 Thalidomide containing regimens

- CTDa (Cyclophosphamide, Thalidomide, attenuated Dexamethasone)
- MPT (Melphalan, Prednisolone, Thalidomide)

3.2.3 Lenalidomide containing regimens

- RDa (Lenalidomide, attenuated Dexamethasone)

3.3 Patients with severe renal failure

Up to 30% of newly diagnosed myeloma patients present with renal impairment (creatinine >200µmol/L). Patients with severe renal failure should be transferred to a centre that is able to provide dialysis if needed.

Early treatment with a bortezomib-based regimen, best combined with Thalidomide and Dexamethasone (no dose adjustments needed), is recommended and may result in recovery of renal function. The use of plasma exchange/ultrafiltration has not consistently been shown to be of benefit.²⁷

For dose adjustment of cytotoxic depending on renal impairment please refer to the following website:

<http://www.eastmidlandscancernetwork.nhs.uk/Library/RenalDosageAdjustments.pdf>

3.4 Relapsed myeloma

Relapse may occur in the same of different plasma cell clone and switch from paraprotein, to light chains (light chain escape) to non-secretory and vice-versa. With each relapse the disease becomes more resistant. Where possible patients should be offered enrolment onto clinical trials.

In principle, triplet combinations are more effective than doublets. Outside trial, the options for salvage therapy include:

3.4.1 First relapse – consider clinical trials where possible

- Daratumumab-Velcade-Dexamethasone for Velcade-responsive disease was NICE approved in 2019 and will provide the best option for most patients
- Lenalidomide-Dexamethasone has been approved by NICE in May 2019 in patients previously treated with Velcade and is a suitable all oral option for patients refractory to Velcade or not keen to attend hospital for chemotherapy
- If Velcade-naïve, Carfilzomib-Dexamethasone is available and showed superiority to Velcade-Dexamethasone in PFS and OS²⁰

- If Velcade was used at presentation with good response, they can be considered for re-treatment at first relapse unless considered unsuitable (e.g. with \geq grade 2 neuropathy)
- If the response to first-line Velcade was inadequate or associated with unacceptable toxicity, combination using Thalidomide, Cyclophosphamide and corticosteroid could be used
- Consolidation with 2nd ASCT can be considered provided the patient is medically fit and first transplant progression-free survival was \geq 12-18 months or ASCT was not used at first response²¹

3.4.2 Second relapse – consider clinical trials where possible

- Ixazomib-Lenalidomide-Dexamethasone is NICE approved at second and third relapse for patients that are not refractory to Lenalidomide and have never received Ixazomib; treatment should be continued to maximal response and steroid dose reduction or cessation could be considered at this point if tolerance is suboptimal
- Lenalidomide-Dexamethasone until disease progression; approved for second or later relapse

Lenalidomide can only be reused if prior treatment was part of clinical trial. The addition of ixazomib significantly prolongs PFS without adding unmanageable side effects. In particular, no increase in peripheral neuropathy has been observed.²²

3.4.3 Third and subsequent relapse

- Ixazomib-Lenalidomide-Dexamethasone; if not used on 3rd line, this can be available on 4th line with the same criteria as per 3rd line
- Panobinostat-Velcade-Dexamethasone; this regimen is recommended as an option after at least 2 prior regimens which include an immunomodulatory agent and bortezomib²³
- Pomalidomide-Dexamethasone; NICE approved after previous treatments with lenalidomide and bortezomib²⁴
- Daratumumab monotherapy; NICE approved as 4th line or later²⁵

Other Options include:

- Bendamustine-Thalidomide-Dexamethasone
- Cyclophosphamide and dexamethasone alone
- CTDa (Cyclophosphamide, Thalidomide, attenuated Dexamethasone)
- Melphalan-Prednisolone
- Methylprednisolone, high-dose

3.5 Novel agents and their side effect profile

3.5.1 Carfilzomib

Carfilzomib is a second-generation proteasome inhibitor that is well tolerated. The commonest toxicities are reversible thrombocytopenia, other cytopenia and fatigue.

Rare complications include cardiotoxicity (distinct features: modest LVEF reduction and increased NT-proBNP but serum troponins are normal). Occurrence is unpredictable, serial echocardiograms are of no use in predicting cardiac events. Serial NT-proBNP levels are an important marker for the diagnosis and monitoring of acute heart failure, including conditions such as AL amyloidosis. Based on current evidence this drug is best avoided in patients with known congestive heart failure.

3.5.2 Daratumumab

This monoclonal anti-CD38 antibody also binds onto red blood cells. Whilst no severe haemolysis has been reported, it has been shown to result in false-positive red cell antibody screening test results in the blood bank in all media (saline, PEG, LISS). The daratumumab effect manifests as a warm autoantibody and will pan-react to any testing carried out including indirect (IAT) and direct antiglobulin tests (DAT), antihuman globulin (AHG) testing, and antibody screening and identification panels. ABO/RhD testing and immediate spin crossmatch is not affected.

3.5.3 Ixazomib

Ixazomib is an oral proteasome inhibitor with a significantly better side effect profile when compared to bortezomib.

3.6 Primary refractory myeloma

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

Patients with primary refractory disease should where possible be considered for early phase clinical trials. Novel combinations of previously received therapies may be appropriate or single agent alkylating agents or corticosteroids with palliative intent.

Combination regimens (e.g. VTD-PACE) can be appropriate in certain settings. The aim should be to get patients to ASCT and also consideration given to tandem AlloSCT in those young and fit patients. Care should be taken in frail patients or patients with poor performance status or co morbidities.

3.7 Solitary plasmacytoma

Please refer to published BCSH guidelines and discuss management at MDT with radiation oncology input as radiotherapy is required.⁴¹

4.0 Assessment of response

4.1 During treatment

- Serum or urine paraprotein quantitation at the start of each treatment cycle and before high dose therapy
- Serum free light chain (SFLC) test can be used for assessment at baseline in all patients, at the start of each cycle and for monitoring for relapse; especially useful in AL amyloidosis and light chain myeloma
- Bone marrow biopsy is particularly useful in oligo-/non-secretory myeloma and can also be performed after completion of induction therapy and prior to stem cell mobilization

4.2 Following HDT and after treatment

- Serum and urine PP or SFLC at two-monthly intervals
- Full blood count (FBC) and urea and electrolytes (U&E)
- Bone marrow assessment at three months and then at relapse if deemed necessary (not usually required as relapse obvious on paraprotein and/or SFLC)

4.3 Definition of response criteria²⁷

Complete remission (CR)	Negative serum/urine immunofixation Disappearance of soft tissue plasmacytomas <5% plasma cells in bone marrow
Stringent complete remission (sCR)	As above plus Normal SFLC ratio and no evidence of clonal plasma cells on immunohistochemistry or flow cytometry
Very good partial response (VGPR)	>90% reduction in serum paraprotein and <100mg/24h BJP
Partial response (PR)	>50% reduction in serum PP and/or >90% reduction in BJP and/or ≥50% decrease in difference between involved and uninvolved SFLC and or >50% decrease in bone marrow plasma cells (if non-secretory myeloma)

Stable disease / no response (SD)	None of the above and no disease progression
Progressive disease (PD)	>25% increase in serum PP (>5g/L) >25% increase in urinary BJP (>200mg/24h) >25% increase in SFLC (>100mg/L) >25% increase in bone marrow plasma cells (>10%) New bone lesions/plasmacytomas Myeloma-related hypercalcaemia
Primary refractory	Defined as having never achieved partial response on therapy (PR) Non-responding, non-progressive Progressive disease (PD)
Relapsed/refractory	Achieved PR but progressed within 60 days
Relapsed	PD after initially achieving PR for >60 days and off therapy

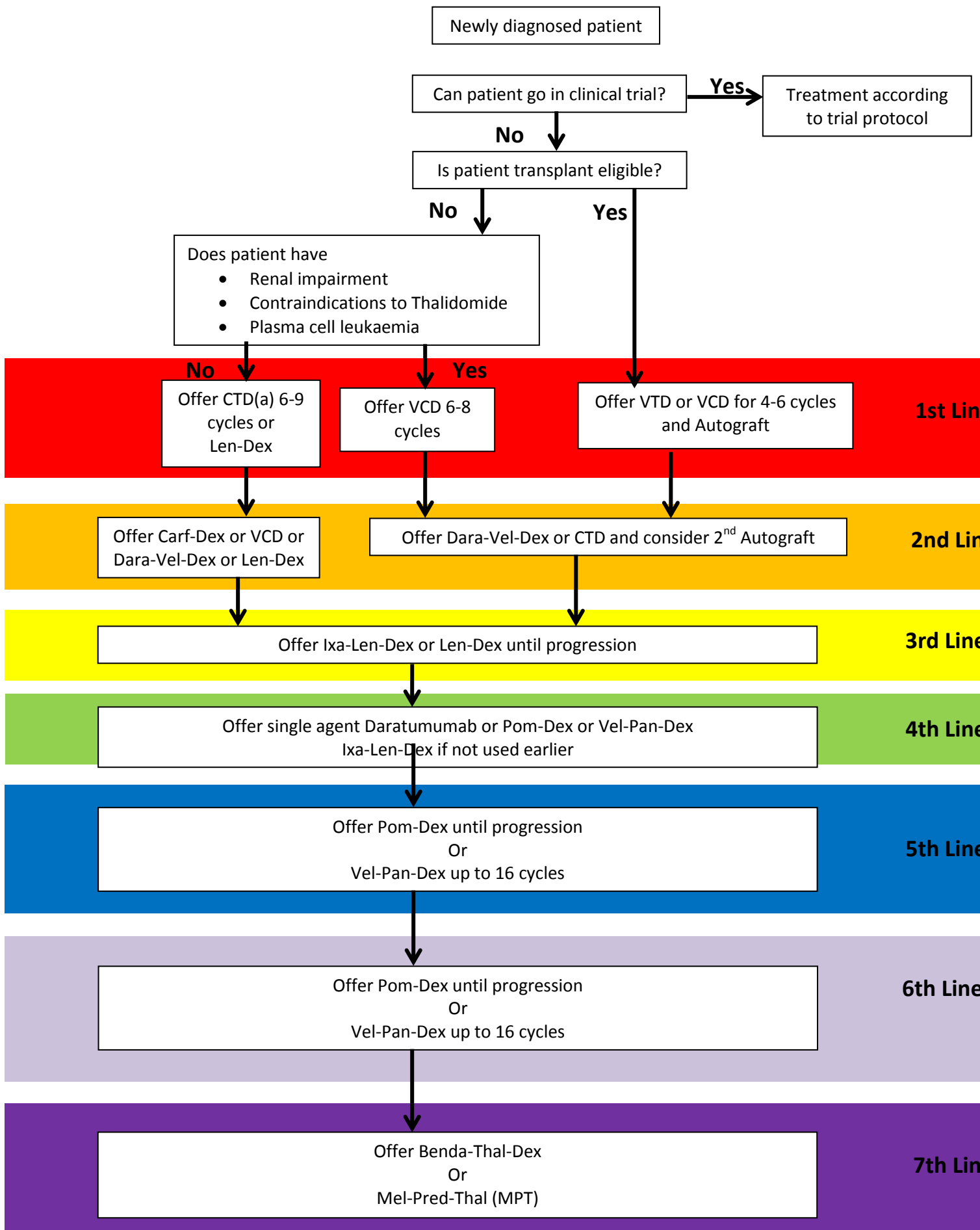
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Appendix 1: Myeloma Treatment Pathway 2019



Appendix 2: Management of myeloma related emergencies and complications

1. Spinal cord compression

It is a medical emergency and requires rapid diagnosis with treatment within 24 hours of presentation. The clinical features and management 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.

- Commence immediately Dexamethasone 8mg bd or methylprednisolone
- Urgent MR spine
- Refer to the on-call clinical oncologist (<24 hours) for consideration of radiotherapy (switch board at The Christie)
- Consider discussion with the on-call neurosurgical team for surgical decompression or the spinal surgeons about spinal stability (both via switch at Salford Royal)

2. Hypercalcaemia

Hypercalcaemia may range from mild to severe but requires urgent attention:

- Aggressive hydration with IV normal saline >3L/day
- Loop diuretics such as Frusemide, especially in renal or heart failure
- IV bisphosphonates (zoledronate or pamidronate) can be repeated after 3-5 days if hypercalcaemia persists.
- Steroids (Dexamethasone 20-40mg)
- Systemic anti-cancer treatment should be initiated rapidly
- Calcitonin is an alternative in treatment resistant patients
- Denosumab as an alternative bisphosphonate can be considered after discussion with endocrinologists

3. Hyperviscosity

Hyperviscosity may develop in patients with a high serum paraprotein and can be associated with blurred vision, headaches, mucosal bleeding and dyspnoea due to heart failure.

When suspected treat as a medical emergency (do not wait for PV result):

- Aggressive hydration with IV normal saline >3L/day
- Dexamethasone 40mg for 4 days followed by systemic anti-myeloma treatment
- In severe cases consider plasmapheresis (1-1.5x plasma volume using saline and albumin replacement)
- If plasmapheresis delayed consider isovolaemic venesection with IV normal saline replacement
- Caution with blood transfusion in symptomatic anaemia, avoid where possible until after plasmapheresis

4. Renal failure

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

- Aggressive hydration with IV normal saline >3L/day
- Avoid nephrotoxic drugs (e.g. non-steroidals, radiographic contrast agents, aminoglycosides)
- Dexamethasone 40mg for 4 days followed by systemic anti-myeloma treatment
- Bortezomib combination regimes (biweekly for first cycle) are preferred in this setting
- Caution with loop diuretics as can exacerbate light chain deposition in AL Amyloidosis

Early involvement of the renal team is recommended, especially if renal function does not improve within 48 hours of rehydration and correction of hypercalcaemia. A 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 early.

5. Infections

Myeloma is associated with an increased risk of infection as a result of deficits in the immune system and as a complication of treatment.

The following prophylactics are recommended:

- Co-trimoxazole or penicillins for bacterial infections
- Aciclovir for HSV and VZV with high dose steroids and proteasome inhibitors

In patients with recurrent chest infections despite antibiotic prophylaxis vaccination with the pneumococcal and HIB vaccine is recommended. In severe cases with persistent infections, IVIG replacement may be considered as per Department of Health guidance (if total IgG level <0.5g/L give 0.4g/kg every 4 weeks).

Febrile events should be treated promptly with broad spectrum antibiotics. Intravenous antibiotics are required for severe infection and neutropenic sepsis as per local policy.

The annual flu vaccine is strongly recommended, irrespective of active treatment.

Appendix 3: Supportive care and common treatment-related complications

Anaemia Is often multifactorial due to marrow infiltration, renal impairment, vitamin deficiency and systemic anti-cancer treatment (SACT) induced marrow suppression. Anaemia often improves following disease control by SACT. Anaemia associated with renal impairment may respond to erythropoietin and should be managed in conjunction with a renal physician.

Note that there is an increased thrombotic risk when erythropoietin is used concurrently with IMiDs and corticosteroids. The choice of thromboprophylaxis should reflect this increased risk.

Bleeding – severe thrombocytopenia Platelets should be transfused when the platelet count $<10 \times 10^9/L$, or $<20 \times 10^9/L$ in the setting of sepsis. If the patient is bleeding, aim for higher platelet counts, depending on extent and site of blood loss.

Bleeding – coagulopathy Coagulopathic states are rare in myeloma but may be associated with dys- or hypo-fibrinogenaemia or the development of specific clotting factor inhibitors. Acquired deficiency of factor X occurs in patients with systemic amyloid light-chain (AL) amyloidosis, presumably due to adsorption of factor X to amyloid fibrils. Thus, aggressive treatment of the underlying plasma cell dyscrasia in AL amyloidosis can lead to the amelioration of amyloid-related factor X deficiency.

Peripheral neuropathy Several chemotherapeutic agents for myeloma can be associated with the development of peripheral neuropathy, particularly bortezomib and thalidomide. Development of symptoms is usually associated with cumulative exposure to these drugs but can occur with minimal exposure. Close monitoring of symptoms and appropriate modification of dosing/schedule are critical to prevent the worsening of nerve damage (see individual treatment protocols for dose adjustments).

Radiotherapy This should always occur following full discussion with clinical oncology colleagues and may be required for spinal cord or cauda equina compression due to myelomatous deposit, painful bony lesion(s) or extramedullary myelomatous deposit(s) not responding to systemic treatment or following surgical stabilisation.

Pain management Analgesia includes simple analgesics (paracetamol), weak opiates (co-codamol, tramadol), strong oral opiates (MST, oxycodone) and opiate patches (fentanyl). Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided. Amitriptyline, gabapentin, duloxetine and pregabalin are useful for treating neuropathic pain. Radiotherapy may be indicated for severe localised pain due to bone infiltration or nerve root compression. Depending on MDT consensus patients could be considered for Vertebroplasty/kyphoplasty for focal vertebral damage causing persistent pain (e.g. wedge collapse) despite SACT/radiotherapy.

Bone disease All patients with symptomatic myeloma should receive zoledronic acid plus oral calcium and vitamin D regardless of whether or not bone lesions are present. The Myeloma IX study reported that zoledronic acid is superior to sodium clodronate in terms of reduced skeletal related events and prolonged progression free and overall survival (6 months advantage) but was associated with an increased risk of osteonecrosis of the jaw (3.5% v 0.3%). IV Zoledronic acid is the bisphosphonate of choice. Suggest dental assessment prior to treatment initiation with regular dental follow-ups and good oral hygiene. Renal function should be carefully monitored with dose reductions in line with SmPC.

The required duration of bisphosphonate therapy has not been defined. In general patients with no active bone disease and prolonged deep disease control post treatment (CR or VGPR), stopping after 2 years should be considered. At time of disease relapse bisphosphonate therapy can be reinstated.

Thromboprophylaxis Patients treated with IMiDs (thalidomide, lenalidomide and pomalidomide) are at an increased risk of thromboembolic events. The highest period of risk is during the first 4-6 months of therapy. All patients should have their thrombotic risk assessed and thromboprophylaxis prescribed; low-risk patients should be prescribed aspirin, high-risk patients LMWH or treatment dose warfarin.

Intravenous immunoglobulins (Ivlg) Routine Ivlg is not recommended. However, patients who suffer from recurrent bacterial infections (≥ 3 bacterial infections/year requiring treatment), who have hypogammaglobulinaemia and have failed a trial of prophylactic antibiotics and vaccination may benefit from monthly infusions of Ivlg (0.4g/kg). Three-monthly review to assess the efficacy of regular Ivlg is required.

Please refer to the National guidelines on Ivlg use - <https://www.england.nhs.uk/wp-content/uploads/2013/04/b09-ps-a.pdf>

Appendix 4: Chemotherapy regimens

Bendamustine-Thalidomide-Dexamethasone

Bendamustine 60mg/m² IV OD Days 1, 8
Thalidomide 100mg PO OD Days 1-28
Dexamethasone 20mg PO OD Days 1, 8, 15, 22
Repeat every 28 days for 6-9 cycles

Keep ANC >1.0x10⁹/L and platelets >75x10⁹/L prior to each dose of Bendamustine

Prophylactics: Allopurinol 300mg PO OD
 PPI with steroids
 Fluconazole 50mg PO OD
 Aciclovir 400mg PO BD
 Co-trimoxazole as per local policy
 Ondansetron 8mg IV/PO BD with Bendamustine (optional)

Thromboprophylaxis with LMWH or full anticoagulation with warfarin is recommended. Aspirin can be considered in low risk cases.³¹

Dose modifications:

1. Myelosuppression - omit Bendamustine and use G-CSF
2. Renal impairment - no change if eGFR >10ml/min
3. Liver impairment - if Bili 20-51umol/L reduce Bendamustine by 30%, if Bili >51umol/L omit Bendamustine

Bortezomib-Dexamethasone²⁸

Bortezomib 1.3mg/m² SC OD Days 1, 4, 8, 11
Dexamethasone 20mg PO OD Days 1-2, 4-5, 8-9, 11-12
Repeat every 21 days for 4-8 cycles

Keep ANC >0.5x10⁹/L and platelets >25x10⁹/L prior to each dose of bortezomib

Monitor for neuropathy using the bortezomib-specific patient questionnaire

Prophylactics:

- Allopurinol 300mg PO OD
- PPI with steroids
- Fluconazole 50mg PO OD
- Aciclovir 400mg PO BD
- Co-trimoxazole as per local policy
- Ondansetron 8mg IV/PO BD with Bortezomib (optional)

Dose modifications:

1. Age/tolerability - give weekly with or without a 1-week break (4- or 5-week cycle); adjust dexamethasone accordingly
2. Renal impairment - none, in dialysis patients give bortezomib after dialysis
3. Neuropathy - see table 3

Table 3: Bortezomib-induced neuropathy grading and dose modifications

Severity of neuropathy	Dose modification
Grade 1 (paraesthesia, weakness, loss of reflexes) with no pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Withhold bortezomib until symptoms of toxicity have resolved
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold bortezomib until symptoms of toxicity have resolved, then restart at reduced dose (0.7mg/m ²) and change treatment schedule to once weekly
Grade 4 (sensory neuropathy which is disabling or motor neuropathy that is life threatening or leads to paralysis) and/or severe autonomic neuropathy	Discontinue bortezomib

Bortezomib-Cyclophosphamide-Dexamethasone¹⁴

Bortezomib 1.3mg/m² SC OD Days 1, 4, 8, 11
Cyclophosphamide 350mg/m² PO OD Days 1, 8, 15 (max 500mg)
Dexamethasone 20mg PO OD Days 1-2, 4-5, 8-9, 11-12
Cycles are repeated every 21 days for 4-8 cycles

Keep ANC >0.5x10⁹/L and platelets >25x10⁹/L prior to each dose of bortezomib

Monitor for neuropathy using the bortezomib-specific patient questionnaire

Prophylactics: Allopurinol 300mg PO OD
PPI with steroids
Fluconazole 50mg PO OD
Aciclovir 400mg PO BD
Co-trimoxazole as per local policy
Ondansetron 8mg IV/PO BD with Bortezomib (optional)

Dose modifications:

1. Age/tolerability - give bortezomib weekly with or without a 1-week break (4- or 5-week cycle); adjust dexamethasone accordingly
2. Renal impairment - consider reducing cyclophosphamide as per SmPC; no adjustment required for bortezomib, in dialysis patients give bortezomib after dialysis
3. Neuropathy - see table 3

Bortezomib-Thalidome-Dexamethasone²⁹⁻³⁰

Bortezomib 1.3mg/m² SC Days 1, 4, 8 and 11
Dexamethasone 40mg OD PO Days 1-4 (cycle 1&2 Days 8-11 also)
Thalidomide 100mg OD PO Days 1-21
Thalidomide dose can be increased to 200mg as tolerated
Cycles are repeated every 21 days

Keep ANC >0.5x10⁹/L and platelets >25x10⁹/L prior to each dose of bortezomib

Monitor for neuropathy using the bortezomib-specific patient questionnaire

Prophylactics:
Allopurinol 300mg PO OD
PPI with steroids
Fluconazole 50mg PO OD
Aciclovir 400mg PO BD
Co-trimoxazole as per local policy
Ondansetron 8mg IV/PO BD with Bortezomib (optional)
Thromboprophylaxis with LMWH or full anticoagulation with warfarin is recommended. Aspirin can be considered in low risk cases.³¹

Dose modifications:

1. Age/tolerability - give bortezomib weekly with or without a 1-week break (4- or 5-week cycle); adjust dexamethasone accordingly
2. Renal impairment - none, in dialysis patients give bortezomib after dialysis
3. Neuropathy - see table 3

Bortezomib-Melphalan-Prednisolone¹⁵

Bortezomib 1.3mg/m² SC OD Days 1, 4, 8, 11, 22, 25, 29, 32 for cycles 1-4
Days 1, 8, 22, 29 for cycles ≥5

Melphalan 9mg/m² PO OD Days 1-4

Prednisolone 60mg/m² PO OD Days 1-4

Repeat every 6 weeks for up to 9 cycles

ANC >1.0x10⁹/L and platelets >75x10⁹/L prior to each cycle

Prophylactics:

Allopurinol 300mg PO OD

PPI with steroids

Fluconazole 50mg PO OD

Aciclovir 400mg PO BD

Co-trimoxazole as per local policy

Ondansetron 8mg IV/PO BD with Bortezomib/Melphalan

Dose modifications:

1. Myelosuppression - dose adjust melphalan as per SmPC
2. Renal impairment - reduce melphalan by 50% if eGFR 30-50ml/min, omit if eGFR <30ml/min; in dialysis patients give bortezomib after dialysis
3. Neuropathy - see table 3

Carfilzomib-Dexamethasone

Carfilzomib 20mg/m² IV OD Days 1, 2 of cycle 1
56mg/m² IV OD Days 8, 9, 15, 16 of cycle 1
Days 1, 2, 8, 9, 15, 16 for cycles ≥2
Dexamethasone 20mg PO OD Days 1, 2, 8, 9, 15, 16, 22, 23
Repeat every 28 days until disease progression or toxicity

Pre- and post-carfilzomib hydration with 500ml 0.9% saline in recommended with cycles 1 (all infusions) and 2 (1st infusion only)

ANC >1.0x10⁹/L and platelets >50x10⁹/L prior to each cycle

Prophylactics: Allopurinol 300mg PO OD
PPI with steroids
Fluconazole 50mg PO OD
Aciclovir 400mg PO BD
Co-trimoxazole as per local policy

Dose modifications:

1. Myelosuppression - omit carfilzomib if ANC <0.5x10⁹/L or platelets ≤10x10⁹/L, restart as per SmPC (see table 4); restart at 1 level lower after ANC >0.5x10⁹/L or platelets >10x10⁹/L
2. Renal impairment - avoid carfilzomib in renal failure

Table 4: Carfilzomib dose reduction

Starting dose	Level 1	Level 2	Level 3
56mg/m ²	45mg/m ²	36mg/m ²	27mg/m ²

Cyclophosphamide +/- Prednisolone⁴⁰

Cyclophosphamide 300mg/m² IV or 400mg/m² PO once weekly
Prednisolone 60mg PO AD for 6 weeks, reducing to zero over 2 weeks
Continued weekly until plateau phase or progression

Dose modifications

1. Renal impairment - reduce cyclophosphamide by 25% if eGFR 10-50ml/min and by 50% if GFR <10ml/min; omit if plasma creatinine >300umol/L

Cyclophosphamide-Thalidomide-Dexamethasone³⁷

Cyclophosphamide 500mg PO OD Days 1, 8, 15
Thalidomide 200-400mg PO OD Days 1-21
Dexamethasone 40mg PO OD Days 1-4, 8-12
Repeat every 21 days to maximal response (6 to 9 cycles)

Cyclophosphamide-Thalidomide-Dexamethasone (attenuated)³⁷

Cyclophosphamide 500mg PO OD Days 1, 8, 15, 22
Thalidomide 100-200mg PO OD Days 1-28
Dexamethasone 20mg PO OD Days 1-4, 15-18
Repeat every 28 days to maximal response (6 to 9 cycles)

Thalidomide related side effects such as severe neuropathy, fatigue, constipation or sedation may require drug discontinuation but can be reintroduced at a lower dose if symptoms subside.

Prophylactics: Allopurinol 300mg PO OD
 PPI with steroids
 Fluconazole 50mg PO OD
 Aciclovir 400mg PO BD
 Co-trimoxazole as per local policy

Thromboprophylaxis with LMWH or full anticoagulation with warfarin is recommended. Aspirin can be considered in low risk cases.³¹

Dose modifications:

1. Myelosuppression - omit/reduce cyclophosphamide
2. Renal impairment - reduce cyclophosphamide by 25% if eGFR 10-50ml/min and 50% if eGFR <10ml/min; omit if creatinine >300umol/L

Daratumumab monotherapy

Cycles 1-2

Daratumumab 16mg/kg IV OD Days 1, 8, 15, 22
Dexamethasone 4mg PO OD Days 2, 3, 9, 10, 16, 17, 23, 24

Cycles 3-6

Daratumumab 16mg/kg IV OD Days 1, 15
Dexamethasone 4mg PO OD Days 2, 3, 16, 17

Cycles ≥ 7

Daratumumab 16mg/kg IV OD Days 1
Dexamethasone 4mg PO OD Days 2, 3

Repeat every 28 days until disease progression or toxicity

Pre-medicate prior to infusion to minimise infusion related reactions; for infusion rates see table 5

Pre-medications: Paracetamol 1g PO
Monteleukast 10mg PO (cycle 1 only)
Chlorphenamine 10mg IV
Dexamethasone 20mg IV/PO (cycles 1-2)
Dexamethasone 12mg IV/PO (cycles 3-6)

Prophylactics: Allopurinol 300mg PO OD
PPI with steroids
Fluconazole 50mg PO OD
Aciclovir 400mg PO BD
Co-trimoxazole as per local policy

Table 5: Daratumumab infusion rates

	0.9% NaCl	Initial rate (1 st hour)	Rate increment	Maximum rate
First infusion	1000ml	50ml/hr	50ml/hr every hr	200ml/hr
Second infusion	500ml	50ml/hr	50ml/hr every hr	200ml/hr
Subsequent infusions	500ml	100ml/hr	50ml/hr every hr	200ml/hr

Daratumumab-Velcade-Dexamethasone

Cycles 1-3

Daratumumab 16mg/kg IV OD	Days 1, 8, 15, 22
Bortezomib 1.3mg/m ² SC OD	Days 1, 4, 8, 11
Dexamethasone 20mg IV/PO OD	Days 1, 2, 4, 5, 8, 9, 11, 12, 15, 16*

Cycles 4-8

Daratumumab 16mg/kg IV OD	Days 1
Bortezomib 1.3mg/m ² SC OD	Days 1, 4, 8, 11
Dexamethasone 20mg IV/PO OD	Days 1, 2, 4, 5, 8, 9, 11, 12*

Cycles ≥9

Daratumumab 16mg/kg IV OD	Days 1
Dexamethasone 12mg IV/PO OD	Days 1*
Dexamethasone 8mg IV/PO OD	Days 2

Repeat every 28 days cycles 1-8, every 28 days until disease progression or toxicity from cycles 9 onwards

Pre-medicate prior to infusion to minimise infusion related reactions; for infusion rates see table 5

*Omit dexamethasone dose if already given as part of pre-medication

Pre-medications:

Paracetamol 1g PO
Monteleukast 10mg PO (cycle 1 only)
Chlorphenamine 10mg IV
Dexamethasone 20mg IV/PO (cycles 1-8)
Dexamethasone 12mg IV/PO (cycles ≥9)

Prophylactics:

Allopurinol 300mg PO OD
PPI with steroids
Fluconazole 50mg PO OD
Aciclovir 400mg PO BD
Co-trimoxazole as per local policy

Dose modifications:

1. Myelosuppression - omit bortezomib if grade 4 toxicity, restart at 25% reduced dose
2. Renal impairment - none, in dialysis patients give bortezomib after dialysis
3. Neuropathy - see table 3 for bortezomib related neurotoxicity

Dexamethasone, pulsed

Dexamethasone 20-40mg PO OD Days 1-4

Repeat every 14 to 21 days

Prophylactics: Allopurinol 300mg PO OD
 PPI with steroids
 Fluconazole 50mg PO OD
 Aciclovir 400mg PO BD
 Co-trimoxazole as per local policy

DT-PACE³²

Dexamethasone 40mg PO OD Days 1-4
Thalidomide 100-200mg PO OD Days 1-28
Cisplatin 10mg/m² IV Days 1-4
Doxorubicin 10mg/m² IV Days 1-4
Cyclophosphamide 400mg/m² IV Days 1-4
Etoposide 40mg/m² IV Days 1-4

Central venous access is required for this regimen. Cisplatin, cyclophosphamide and etoposide are combined in 1 litre of 0.9% saline and given together as a continuous iv infusion over 24 hours. Doxorubicin is infused separately in 250ml 5% dextrose.

Repeat every 4 to 6 weeks; the number of cycles is to be discussed with the transplant centre

ANC >1.0x10⁹/L and platelets >100x10⁹/L required prior to each cycle

Prophylactics: G-CSF from Day 5 until ANC >1.0x10⁹/L
 Allopurinol 300mg PO OD
 PPI with steroids
 Fluconazole 50mg PO OD
 Aciclovir 400mg PO BD
 Co-trimoxazole as per local policy
 Ciprofloxacin 500mg PO BD
 Ondansetron 8mg IV/PO BD

Thromboprophylaxis with LMWH or full anticoagulation with warfarin is recommended. Aspirin can be considered in low risk cases.³¹

Dose modification

1. Renal impairment - Creatinine clearance must be >50ml/min prior to each course

Ixazomib-Lenalidomide-Dexamethasone

Ixazomib 4mg PO OD Days 1, 8, 15
Lenalidomide 25mg PO OD Days 1-21
Dexamethasone 40mg OD PO Days 1, 8, 15, 22
Repeat every 28 days until disease progression or toxicity

ANC $>1.0 \times 10^9/L$ and platelets $>70 \times 10^9/L$ required prior to each cycle

Dose modification

1. Myelosuppression - omit/reduce ixazomib / lenalidomide as per SmPC
2. Renal impairment - reduce ixazomib to 3mg if eGFR $<30 \text{ml/min}$ (safe in dialysis)
3. Neurotoxicity - omit ixazomib with any signs of neuropathy, restart once resolves

Lenalidomide-Dexamethasone³⁸⁻³⁹

Len-Dex (high-dose)

Lenalidomide 25mg PO OD Days 1-21
Dexamethasone 40mg PO OD Days 1-4, 9-12, 17-20 for cycles 1-4
Days 1-4 for ≥ 5 cycles

Len-dex (attenuated-dose)

Lenalidomide 25mg PO OD Days 1-21
Dexamethasone 40mg PO OD Days 1, 8, 15, 22
Repeat every 28 days until disease progression or toxicity

Prophylactics:
Allopurinol 300mg PO OD
PPI with steroids
Fluconazole 50mg PO OD
Aciclovir 400mg PO BD
Co-trimoxazole as per local policy

Thromboprophylaxis with LMWH or full anticoagulation with warfarin is recommended. Aspirin can be considered in low risk cases.³¹

Dose modifications:

1. Myelosuppression - use GCSF where possible and continue full dose; if severe reduce lenalidomide as per SmPC
2. Renal impairment - reduce lenalidomide as per SmPC

Lenalidomide-Cyclophosphamide-Dexamethasone

Lenalidomide 25mg PO OD Days 1-21
Cyclophosphamide 500mg PO Days 1, 8
Dexamethasone 40mg PO OD Days 1, 8, 15, 22
Repeat every 28 days until progression or toxicity

Prophylactics: Allopurinol 300mg PO OD
 PPI with steroids
 Fluconazole 50mg PO OD
 Aciclovir 400mg PO BD
 Co-trimoxazole as per local policy

Thromboprophylaxis with LMWH or full anticoagulation with warfarin is recommended. Aspirin can be considered in low risk cases.³¹

Dose modifications:

1. Myelosuppression - use GCSF where possible and continue full dose; if severe reduce lenalidomide as per SmPC; omit/reduce cyclophosphamide
2. Renal impairment - reduce lenalidomide as per SmPC

Melphalan-Prednisolone³⁴

Melphalan 7mg/m² PO OD Days 4-5
Prednisolone 50mg PO OD Days 4-5
Repeat every 4-6 weeks until maximal response (plateau phase) and continued for three further cycles thereafter (usually 6 to 9 cycles)

ANC > 1.0x10⁹/L and platelets >75x10⁹/L prior to each cycle

Prophylactics: Allopurinol 300mg PO OD
 PPI with steroids
 Fluconazole 50mg PO OD
 Aciclovir 400mg PO BD
 Anti-emetics as required

Dose modifications:

1. Myelosuppression - reduce to 3-4 days of melphalan³⁵
2. Renal impairment - eGFR 30-50ml/min reduce melphalan by 50%, if eGFR <30ml/min avoid melphalan

Melphalan-Prednisolone-Thalidomide³⁶

Melphalan 4mg/m² PO OD Days 1-7

Prednisolone 40mg/m² PO OD Days 1-7

Thalidomide 100mg PO OD Days 1-28

Repeat every 4-6 weeks for 6 cycles or until maximal response (plateau phase);

Thalidomide is continued as maintenance for further 6 months

ANC > 1.0x10⁹/L and platelets >75x10⁹/L prior to each cycle

Prophylactics: Allopurinol 300mg PO OD

 PPI with steroids

 Fluconazole 50mg PO OD

 Aciclovir 400mg PO BD

 Anti-emetics as required

Thromboprophylaxis with LMWH or full anticoagulation with warfarin is recommended. Aspirin can be considered in low risk cases.³¹

Dose modifications:

1. Myelosuppression - reduce to 3-4 days of melphalan³⁵
2. Renal impairment - eGFR 30-50ml/min reduce melphalan by 50%, if eGFR <30ml/min avoid melphalan

Thalidomide related side effects such as thrombo-embolism or severe neuropathy, fatigue, sedation or constipation may require its discontinuation. It may be re-introduced at a lower dose of 50mg at a later date if symptoms subside.

Panobinostat-Bortezomib-Dexamethasone

Cycles 1-8

Bortezomib 1.3mg/m² SC Days 1, 4, 8, 11
Dexamethasone 20mg OD PO Days 1, 2, 4, 5, 8, 9, 11, 12
Panobinostat 20mg OD PO Days 1, 3, 5, 8, 10, 12

Cycles ≥9

Bortezomib 1.3mg/m² SC Days 1, 8
Dexamethasone 20mg OD PO Days 1, 2, 8, 9
Cycles are repeated every 21 days for 8 to max 16 cycles

Keep ANC >1.0x10⁹/L and platelets >100x10⁹/L prior to each dose of bortezomib

Monitor for neuropathy using the bortezomib-specific patient questionnaire

Prophylactics:

Allopurinol 300mg PO OD
PPI with steroids
Fluconazole 50mg PO OD
Aciclovir 400mg PO BD
Co-trimoxazole as per local policy
Ondansetron 8mg IV/PO BD with Bortezomib (optional)

Dose modifications:

1. Myelosuppression - omit/reduce bortezomib and Panobinostat as per SmPC
2. Renal impairment - none, in dialysis patients give bortezomib after dialysis
3. Hepatic impairment - reduce Panobinostat as per SmPC
4. Neuropathy - see table 3

Pomalidomide-Dexamethasone²⁴

Pomalidomide 4mg PO OD Days 1-21

Dexamethasone 40mg PO OD Days 1,8,15, 22

Repeat every 28 days until disease progression or toxicity

Prophylactics:

Allopurinol 300mg PO OD

PPI with steroids

Fluconazole 50mg PO OD

Aciclovir 400mg PO BD

Co-trimoxazole as per local policy

Thromboprophylaxis with LMWH or full anticoagulation with warfarin is recommended. Aspirin can be considered in low risk cases.³¹

Dose modifications:

1. Myelosuppression - omit/reduce pomalidomide as per SmPC
2. Renal impairment - omit/reduce pomalidomide as per SmPC

VDT-PACE³³

Bortezomib 1mg/m ² SC OD	Days 1, 4, 8, 11
Dexamethasone 40mg PO OD	Days 1-4
Thalidomide 100-200mg PO OD	Days 4-28
Cisplatin 10mg/m ² IV	Days 1-4
Doxorubicin 10mg/m ² IV	Days 1-4
Cyclophosphamide 400mg/m ² IV	Days 1-4
Etoposide 40mg/m ² IV	Days 1-4

Central venous access is required for this regimen. Cisplatin, cyclophosphamide and etoposide are combined in 1 litre of 0.9% saline and given together as a continuous iv infusion over 24 hours. Doxorubicin is infused separately in 250ml 5% dextrose.

Repeat every 4 to 6 weeks; number of cycles to be discussed with transplant centre

ANC >1.0x10⁹/L and platelets >100x10⁹/L required prior to each cycle

Prophylactics:

- G-CSF from Day 5 until ANC >1.0x10⁹/L
- Allopurinol 300mg PO OD
- PPI with steroids
- Fluconazole 50mg PO OD
- Aciclovir 400mg PO BD
- Co-trimoxazole as per local policy
- Ciprofloxacin 500mg PO BD
- Ondansetron 8mg IV/PO BD

Thromboprophylaxis with LMWH or full anticoagulation with warfarin is recommended. Aspirin can be considered in low risk cases.³¹

Dose modifications:

1. Renal impairment - Creatinine clearance must be measured and >50ml/min prior to each course
2. Neuropathy - see table 3