GUIDELINES FOR THE MANAGEMENT OF

MULTIPLE MYELOMA

AND

RELATED DISORDERS

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MULTIPLE MYELOMA AND RELATED DISORDERS

National guidelines are now revised under the auspices of the BCSH and the UKMF, covering most aspects of myeloma, AL amyloidosis, solitary plasmacytoma of bone, extramedullary plasmacytoma and monoclonal gammopathy of undetermined significance (MGUS). The Regional Guidelines address similar issues but contain more detail in certain areas e.g. drug regimens, recommendations for trials etc. They should be read in conjunction with the National Guidelines which are listed on the BCSH and UKMF websites (www.bcshguidelines.com and www.ukmf.org.uk).

1.0 DIAGNOSTIC CRITERIA

Diagnostic criteria for multiple myeloma:

- ≥10% plasma cells in bone marrow

And at least one of the following:

- Lytic lesion(s) on plain x-rays
- A paraprotein in serum and/or urine (and/or overproduction or abnormal κ/λ ratio of serum free light chains).

Diagnostic criteria for plasmacytoma of bone:

- Low level plasma cell infiltration of bone marrow (<5%)
- One or more lytic lesions on plain x-rays
- Absent or low level paraprotein and/or light chains in serum and/or urine
- No evidence of end-organ damage due to plasma cell dyscrasia

Diagnostic criteria for extramedullary plasmacytoma:

- Low level plasma cell infiltration of bone marrow (<5%)
- Absent or low level paraprotein and/or light chains in serum and/or urine
- No evidence of end-organ damage/lytic lesions due to plasma cell dyscrasia

Diagnostic criteria for monoclonal deposition disease, including amyloidosis:

- Low level plasma cell infiltration of bone marrow (<10%)
- Interstitial protein deposition on tissue biopsy (e.g. rectal/renal biopsy for Congo-red stain)
- Low level paraprotein and/or light chains in serum and/or urine

2.0 INVESTIGATIONS

Peripheral blood

- Full blood count (FBC) and plasma viscosity (PV)
- Serum urea & electrolytes (U&Es)
- Corrected serum calcium
- Serum albumin (prognostic) and uric acid
- Serum electrophoresis, including immunofixation to confirm and type paraprotein
- Quantitation of serum immunoglobulins and paraprotein
- Serum free light chains (sFLC), particularly indicated in patients with no detectable paraprotein in serum, suspected light chain disease, AL Amyloidosis, non-secretory myeloma, IgD myeloma or plasmacytoma (available at immunology department at Manchester Royal Infirmary and Hope Hospital). NB: High coefficient of variation for sFLC, & significant batch/platform variation.
- Beta 2 microglobulin & C-reactive protein (CRP) (prognostic markers)
- Serum vitamin B12 and folate

Urine

- Urine electrophoresis (Bence Jones protein), including immunofixation
- 24 hour urine for creatinine clearance (or eGFR)
- Quantitation of urinary free light chain (uFLC) excretion if present; measured directly on a 24 hour urine collection (available at Christie biochemistry department)

Bone marrow

- Bone marrow aspirate & trephine
- Clonality studies by immunohistochemistry on trephine, and aspirate flow cytometry (CD19; CD56; CD138 etc) may be helpful in patients where the diagnosis is unclear
- Prognostic information may be added by cytogenetic/FISH analysis: t(4;14), t(4;16), t(14;20) by FISH and/or gain 1q, deletion 1p, deletion 13 (esp. in combination) by cytogenetics are of poor prognosis and may suggest shorter remission; hyperdiploidy (esp. trisomies odd-numbered chromosomes) and t(11;14) are associated with better risk disease (although latter seen in Plasma Cell Leukaemia). Cytogenetic service at Christie are happy to liase about samples & prognostic value of testing (Dr Nick Telford).

Imaging studies

- Skeletal survey: standard x-rays of the skeleton including lateral & AP cervical, thoracic and lumbar spine, skull, chest, pelvis, humeri and femora (Radionuclide bone scanning is not usually helpful)
- MR imaging is the diagnostic procedure of choice for patients with suspected spinal cord or nerve root compression
- MR imaging of spine can be performed for exclusion of multiple plasmacytomas & confirmation of true solitary bone plasmacytoma; MR imaging may also be helpful to detect bone disease in selected patients who remain symptomatic despite normal skeletal survey or to clarify an ambiguous CT finding
- CT scanning is not routinely indicated but is helpful for imaging extramedullary disease or for cord compression when MR scan is contra-indicated or not available
- PET scanning may be useful to assess extent/activity of extramedullary disease in individual cases but is not routinely recommended in the management of all myeloma patients (NB: do not perform within 4 weeks of chemotherapy or 3 months of radiotherapy)

Other

- Determination of amyloid type by immunohistochemical methods on tissue biopsy and DNA analysis / amyloid fibril sequencing (available at the Amyloidosis Centre at the Royal Free Hospital, London)
- ECG, Echocardiogram (typical diastolic cardiac dysfunction is seen in amyloidosis), pro-BNP (prognostic in cardiac amyloid)
- SAP scan (available at the Amyloidosis Centre at the Royal Free Hospital, London)

3.0 STAGING SYSTEMS

All newly diagnosed patients with a plasma cell disorder should be staged using the International Staging System (ISS), (+/- Durie-Salmon Staging (DSS) required by the transplant centres when reporting data to EBMT).

3.1 International Staging System (ISS)

Stage I	Beta 2 microglobulin < 3.5 mg/l & Albumin ≥ 3.5 g/dl
Stage II	Neither stage I nor stage III
Stage III	Beta 2 microglobulin ≥ 5.5 mg/l

3.2 Durie Salmon Staging (DSS)

Stage I	All of the following:	• Haemoglobin >10g/dl • Serum calcium < 2.6mmol/l • Normal skeletal survey or solitary bone plasmacytoma only • PP: IgG <50g/l; IgA <30g/l • Bence Jones protein <4g/24h
Stage II	Neither stage I nor stage III	
Stage III	One or more of the following:	• Haemoglobin <8.5g/dl • Serum calcium >3.0mmol/l • Advanced lytic bone lesions • PP: IgG >70g/l; IgA >50g/l • Bence Jones protein >12g/24h

A: Relatively normal renal function (serum creatinine <200mmol/l)

B: Abnormal renal function (serum creatinine ≥200mmol/l)

4.0 DISEASE MONITORING AND ASSESSMENT

Disease should be monitored at regular intervals in all asymptomatic patients not requiring treatment, and response to chemotherapy should be assessed in those on treatment after each cycle:

- FBC, U&Es, corrected calcium and total globulin
- Serum immunoglobulins and paraprotein quantitation for patients with measurable serum paraprotein (except for those with IgD paraprotein who require sFLC monitoring).
- 24 hour urinary light chain quantitation for BJ positive patients.
- sFLCs particularly for light chain disease, AL Amyloidosis, non-secretory/oligosecretory myeloma, IgD myeloma & plasmacytoma (often useful in overall disease/response-monitoring as change is more rapid/sensitive than intact Ig).
- Annual bone marrow aspiration/trephine and full skeletal survey (+/- CT/MRI/PET scan) may be required for monitoring of *non-secretory* myeloma, if sFLC assay is normal.
- MRD may be measured by flow cytometry and has been shown to predict progression free survival. Currently there is no routine regional service available for this but may be requested at HMDS.

If the patient has failed to achieve a partial response after 3 cycles or progressed on therapy, alternative therapy should be considered. If a response is seen, treatment should usually be given until maximum response or plateau is achieved, provided tolerant of side-effects.

4.1 Myeloma Monitoring Sheet

See next page

MYELOMA MONITORING SHEET

NAME …… **DOB** …….. **HOSP NO** ……. **DIAGNOSIS** ……..

DATE	HB	PLT	WCC	Neu	Ig	PP	U	Cr	Ca	sFLC	uBJP	TREATMENT	INVESTIGATIONS / COMMENTS

4.2 Assessment of Response Criteria According to EBMT/IBMTR

Relapse from CR	Reappearance of disease in patients with previous CR
Progressive disease (PD)	New ROTI, increase in serum/urine paraprotein by ≥25% (minimum increase 5g/l SPEP or 200mg/24hr uFLC) or bone marrow plasma cells by ≥25%
Plateau	Stable (+/-24%) serum/urine paraprotein in 3 months
Unchanged/stable disease	Neither consistent with PD or minimal response
Minimal response (MR)	25-49% reduction in serum paraprotein/50-89% reduction urine Bence-Jones Protein
Partial response (PR)	50-89% reduction in serum/urine paraprotein (& uBJP excretion ≤200mg/24hrs)
Very good PR (VGPR)	≥90% reduction in serum/urine paraprotein (& uBJP ≤100mg/24hr)
Near complete response (nCR)	No measurable paraprotein in serum/urine by electrophoresis but present on immunofixation, and/or ≥5% plasma cells on bone marrow
Complete response (CR)	No paraprotein in serum/urine by immunofixation and <5% plasma cells on bone marrow
*Stringent CR (sCR)***(IMWP)**	No paraprotein in serum/urine by immunofixation, normal SFLC, and <5% plasma cells on bone marrow

5.0 INDICATIONS FOR TREATMENT

5.1 Asymptomatic Patients

- Chemotherapy treatment should be delayed until there are signs of progression to end-organ damage
- Active monitoring (3-6 monthly) required

Some patients may fulfil the diagnostic criteria for myeloma but are asymptomatic and may subsequently run a very indolent course. These patients have no symptoms, normal Hb, calcium and renal function and no x-ray bone lesions. Risk of

transformation to symptomatic myeloma is dependent upon degree of plasma cell infiltration, level of paraprotein, sFLC ratio, & in research setting proportion of malignant plasma cells (by FACS). Early alkylator intervention has shown no benefit in 2 historical randomised controlled trials. Clinical trials investigating the role of immunomodulatory drugs are promising and presently one using Lenalidomide suggests survival advantage. However, this is not considered standard practice of care and currently not recommended outside clinical trials. It is therefore appropriate to manage such patients by observation of the paraprotein/sFLC level and end-organ function. Trial of Anti-IL6 antibody (CNTO328) set up for high-risk (>30g/l) asymptomatic myeloma at Christie 2012.

5.2 Symptomatic Patients

- Treatment is indicated for patients with symptoms or evidence of Myeloma-Related Organ or Tissue Impairment (**ROTI**):

Hyper**C**alcaemia	Corrected Ca^{2+} >0.25mmol/l above normal or >2.75 mmol/l
Renal insufficiency	Attributable to myeloma (may need biopsy)
Anaemia	Haemoglobin 20 g/L below normal (or Hb <100 g/L)
Bone lesions	Lytic lesion(s), compression fractures or osteoporosis (attributable to myeloma)

Other:
Symptomatic hyperviscosity
AL amyloidosis
Recurrent bacterial infections (> 2 episodes in 12 months)
Paraprotein related neuropathy

6.0 GENERAL SUPPORTIVE TREATMENT

6.1 Symptomatic

Optimal general management should be a key part of the overall care plan. Patients should be informed appropriately about their condition, its potential complications and the importance of supportive measures. They should be given written information e.g. Myeloma UK, BACUP or LRF booklets, and if appropriate informed of patient support organisations as listed below.

ORGANISATION	TELEPHONE NUMBER	WEBSITE ADDRESS
Myeloma UK	0800 980 3332	www.myeloma.org.uk
BACUP	0800 800 1234	www.cancerbacup.org.uk
LRF	0207 242 1488	www.leukaemia-reasearch.org.uk

6.1.1 Renal function

Maintain adequate hydration (fluid intake of at least 3 litres per day) in all patients, as this preserves renal function. Avoid potentially nephrotoxic drugs (e.g. non-steroidals, radiographic contrast agents, aminoglycosides). If the patient has established renal failure, management should involve a renal physician; more detailed guidance is contained in the BCSH/UKMF guidelines at www.bcshguidelines.org.

6.1.2 Hypercalcaemia

Vigorous fluid replacement with intravenous normal saline, and an intravenous bisphosphonate (e.g. Pamidronate 90mg or Zoledronate 4mg) is recommended. Zoledronic acid shows greater efficacy in RCTs, but is more nephrotoxic. Bisphosphonate therapy may need to be repeated after 5 days if hypercalcaemia is not controlled; this is usually only necessary in patients with aggressive relapse. Corticosteroids may also aid control of hypercalcaemia. A loop diuretic is not of additional benefit unless there is volume overload.

6.1.3 Bone disease and pain management

There should be an active approach to pain control; it can be helpful to enlist the support of palliative care teams, pain specialists and Macmillan nurses in obtaining pain control for myeloma patients.

General measures: It is important to maintain mobility as immobility increases bone loss and the risk of infection as well as impairing quality of life. Physiotherapy and aids such as spinal supports may be useful.

Analgesia: A variety of analgesics may be used, including simple analgesics (Paracetamol 1g qds), weak opiates (Co-codamol 8/500 or 30/500 two tablets qds, Tramadol 50-100mg qds), strong opiates (MST, Hydromorphone, Oxycontin and Fentanyl). A variety of delivery methods exist for the strong opiates incl. buccal, sublingual & transdermal routes. NSAIDs should be avoided in patients with renal

impairment and used with caution in other patients. Neuropathic pain may require atypical analgesics (Amitriptyline, Gabapentin, Pregabalin, Carbamazepine).

Chemotherapy and radiotherapy: Response to chemotherapy is a major factor in reducing progression of bone disease. Local radiotherapy may be of benefit in patients with localised severe pain due to disease or nerve root compression which has not responded to systemic treatment (see radiotherapy section 11.0).

Orthopaedic surgery: Fixation of long bones may be required to treat or prevent pathological fracture. Radiotherapy given post operatively may also improve outcome and is recommended within 2-4 weeks post surgery.

Vertebroplasty/Kyphoplasty: These emerging procedures are usually performed by interventional radiologists and may be indicated for patients with focal vertebral damage causing persistent pain despite other therapy. MR scan is required prior to the procedure and should be requested at time of referral, informing radiology of planned procedure to ensure special imaging views. Both procedures can be performed at Manchester Royal Infirmary; referrals should be sent to Dr Pete Selby, Consultant Physician, with a copy to Dr Rick Whitehouse, Consultant Radiologist. Vertebroplasty is also offered at Hope Hospital (Dr Herwadkar, Consultant Neuroradiologist) and Preston Royal Infirmary (Dr Ali, Consultant Radiologist).

6.1.4 Spinal cord compression

Malignant infiltration of the vertebrae/paravertebral tissues or bony collapse can cause spinal cord compression. Management requires urgent investigation with MR scanning to define the site and extent of tumour; CT scanning is less satisfactory but may be used if MR is unavailable or contra-indicated. Dexamethasone should be commenced immediately (16-40mg daily). Local radiotherapy is the treatment of choice and should be discussed as early as possible (<24 hours) with the on-call Radiation Oncologist at The Christie; there is no advantage in outcome for surgical treatment in the absence of spinal instability.

6.1.5 Anaemia

Many patients are mildly anaemic at diagnosis or become anaemic at some stage of their disease. Causes include marrow infiltration, renal impairment, folate deficiency, marrow suppression following chemotherapy or a combination of these factors. Whilst the Hb of many patients will rise as disease is controlled by treatment, a proportion will

remain anaemic. For symptomatic newly diagnosed patients regular blood transfusions are the treatment of choice.

Erythropoietin (EPO) may be considered in patients with persistent transfusion dependant anaemia despite control of their myeloma, those for whom blood transfusions are not acceptable for religious reasons, and iron-overloaded patients. If anaemia is related to persistent renal impairment, initiation of EPO is recommended at renal dose. Patients with delayed engraftment or engraftment failure post stem cell transplant (SCT) may also be considered for EPO. EPO is currently not approved by NICE for treatment of chemotherapy-induced anaemia, unless very severe with transfusion contraindicated (www.nice.org.uk).

Dose EPO as a thrice weekly (renal) or once weekly injection starting at:

- α-EPO (Neorecormin) 30,000 u/week,
- β-EPO (EPREX) 40,000 u/week or
- Pegylated-β-EPO (Aranesp) 2.25 mcg/kg every 3 weeks

Caution is recommended in patients with uncontrolled hypertension or other active vascular risk factors for thromboembolic disease due to the cardiovascular risks of EPO. To minimise these frequent monitoring and titration to a Hb of <12g/dl is advised.

Baseline studies prior to commencing EPO should include haematinics (vitamin B12, folate, ferritin), FBC, reticulocytes, renal function and blood pressure. Serum EPO levels have been proposed as predictors of response. Therapy should be monitored by FBC, biochemistry, ferritin and blood pressure.

If an inadequate response is observed after week 4, double the dose may be tried for further 4 weeks before non-response is diagnosed. A brisk hypochromic reticulocyte response at 1-2 weeks is common, and patients may feel better before the Hb rises.

6.1.6 Infection

Patients with myeloma are immunosuppressed as a result of both the disease and its treatment. Influenza vaccination should be given to all patients with myeloma annually in Primary Care in line with NHS recommendations, although responses to vaccination may be suboptimal. In patients with recurrent respiratory tract infections, vaccination against pneumococci and haemophilus influenza B, as well as antibiotic prophylaxis may be beneficial (e.g. penicillin V or macrolides). Post-transplant vaccination is also advisable, as per current EBMT/IBMTR guidelines. Myeloma patients are prone to herpetic viruses, esp. Zoster, & acyclovir prophylaxis should be considered when on

therapy (esp. steroid/Bortezomib) & after transplant. TEAM is a UK NCRN RCT of adjunctive quinolone prophylaxis at induction of myeloma (2012).

Intravenous Immunoglobulins: Patients in plateau phase post chemotherapy who suffer from recurrent infections despite vaccination and prophylactic antibiotics may benefit from monthly infusions of IVIg (0.4g/kg) if significantly hypogammaglobulinaemic. Patients must be selected carefully and risks/benefits considered as IVIg supply is decreasing (www.intravenousimmunoglobulin.org for guidance), & idiosyncratic side-effects can occur including vascular events.

6.1.7 Hyperviscosity

High levels of paraprotein can lead to increased plasma viscosity. Symptomatic patients should be treated urgently with plasma exchange; isovolaemic venesection may be used if plasma exchange facilities are not available. If transfusion is urgently required exchange transfusion should be performed. Chemotherapy should be instituted promptly. Asymptomatic patients with minor rises are not an indication for intervention.

6.2 Bisphosphonates

Long-term bisphosphonate therapy is recommended to reduce skeletal-related events for all patients requiring treatment for their myeloma, whether or not bone lesions are evident. Special consideration must be given to patients with severe renal failure. A dental assessment prior to treatment initiation is recommended with regular follow up visits and good oral hygiene to prevent osteonecrosis of the jaw (ONJ).

Oral *clodronate* (1600mg daily) - 50% dose reduction if creatinine clearance 10-30ml/min, contraindicated if creatinine clearance <10ml/min

IV *pamidronate* (90mg monthly over 1.5 hours) - reduce infusion rate to 20mg/hr in severe renal impairment & consider dose-reduction in accordance renal guidance.

IV *zoledronate* (4mg monthly over 15 minutes) - not recommended if serum creatinine >265mmol/l

Table 1: Dose modification of zoledronate for renal impairment

Baseline Creatinine Clearance (ml/min)	*Zoledronate* - recommended dose
> 60	4.0 mg
50 – 60	3.5 mg
40 – 49	3.3 mg
30 – 39	3.0 mg

Calcium and vitamin D supplementation may prevent hypocalcaemia, which is seen following bisphosphonate use in patients with renal impairment. It is also recommended with long-term bisphosphonate use (in particular with zoledronate SPC) for the prevention of skeletal-related events (SRE). All other bisphosphonates are ineffective in myeloma and should not be used. The MRC Myeloma IX trial has data on randomisation between clodronate and zoledronate: Zoledronate from induction reduces SRE over clodronate, even in those with no bony disease at diagnosis[1], and prolongs progression-free & overall survival.in those with bony disease; zoledronate also increased depth of remission (VGPR/CR) in non-intensive arm patients. Zoledronic acid is therefore the recommended initial bisphosphonate in those who have no contraindication (renal/dental). The use of bisphosphonates in myeloma is covered in detail in the BCSH/UKMF guidelines (www.bcshguidelines.com).

Reports of ONJ occurring in bisphophonate-treated patients have led to concerns about long-term treatment. The reported incidence is variable; a higher rate with zoledronate has been suggested in retrospective series & MRC Myeloma IX trial has 3.6% incidence of ONJ in Zoledronate arm & 0.3% in Clodronate arm at median 3.7 years. Duration of bisphosphonate treatment together with trauma (invasive procedures and denture-abrasion) and concomitant infection are suggested risk factors. Dental extractions should be avoided where possible whilst on treatment, & regular check-ups are advised; ideally patients should have dental review before embarking on long-term bisphosphonates. Furthermore, there is no clear guidance regarding length of bisphosphonate therapy; most previous trials of SRE reduction stopped at 2 years. Opinion leaders had therefore suggested consideration of cessation of intravenous bisphosphonates after 1-2 years in patients whose myeloma is in good remission. However the MRCIX trial continued bisphosphonate until intolerance or progression; although minority of patients remained on randomised bisphosphonate at 3.7 year follow-up, there were more late ONJ in patients continuing zoledronic acid beyond 2 years than clodronate. Pragmatically in patients in CR/nearCR after at least 2 years zoledronic acid, either reduction in frequency to 3-monthly intravenous bisphosphonates or switch to oral clodronate (licensed for up to 4 years) is not unreasonable until clearer information is forthcoming regarding optimal duration of IV bisphosphonate therapy, and cumulative ONJ risk. If ceased/reduced, regular bisphosphonate should be resumed at relapse/progression. Those with significant residual disease or severe bone damage may benefit from more frequent bisphosphonate infusions. This is based on expert opinion (Level IV evidence).

7.0 CHEMOTHERAPY

Myeloma is still considered incurable except with full-intensity allograft, and the goals of treatment are that of disease control and prolonged survival whilst preserving good quality of life. Patients requiring treatment should be considered for entry into clinical trials wherever possible. Currently NCRN MRC Myeloma X & Myeloma XI trials are open.

7.1 First line chemotherapy

The choice of 1st line chemotherapy depends on the patient's suitability for subsequent transplantation. Therefore all patients should be divided into two groups according to their suitability which depends on age, performance status and co-morbidities.

In general, patients <70 years of age are suitable for stem cell transplantation; those aged <45 years with an HLA-identical sibling may be considered for myeloablative allogeneic sibling transplant, whilst those of older age or without matching donor are suitable for high-dose therapy and autologous stem cell rescue. Most patients aged >70 years and those of any age with severe co-morbidities are unsuitable for stem cell transplantation. If in doubt of patient's suitability for transplantation, please discuss with the relevant transplant physician early in the treatment process.

7.1.1 Clinical trials

Myeloma XI – A large multi-centre Phase III induction trial, randomising newly diagnosed patients to Lenalidomide vs Thalidomide containing regimens (CTD vs CRD, & CTDa vs CRDa) and Bortezomib-based salvage/consolidation for suboptimal response, together with randomised Lenalidomide maintenance. Currently open at many NorthWest MDT centres incl. Christie, MRI, Salford. South Manchester, Stepping Hill & Trafford.

Eulite – A multicentre Phase II trial in patients presenting with severe renal failure, combining Bortezomib-based induction with rapid light-chain removal via Gambro filtration. Open at Manchester Royal Infirmary.

7.1.2 Off trial - Patients ≤70 years and SUITABLE for stem cell transplantation

If high dose therapy is considered appropriate, rapid cytoreductive chemotherapy without compromising stem cell mobilisation should be used.

Thalidomide and Dexamethasone combined with Cyclophosphamide (CTD) gives higher initial overall response rate than VAD, especially CR, remaining superior post

autograft (CR=50%). Data from *Myeloma IX*, a large multi-centre trial, shows that VGPR and CR rates are significantly higher following CTD than following C-VAD, both pre- & post-autologous stem cell transplant.[2] Vincristine, adriamycin and dexamethasone +/- cyclophosphamide (VAD/C-VAD) was the most widely used regimen, and previous standard of care in the UK. As higher VGPR and CR rates following autologous SCT post VAD are associated with improved EFS and OS, CTD as initial therapy prior to such procedures may result in improved long-term outcomes, but as yet EFS/OS are not significantly different (but late trend to improved survival seen in standard-risk disease). In light of these findings the advantages of CTD as well as increased remission depth mean it is main regimen used in UK. CTD avoids alopecia, emesis, central access, anthacycline cardiotoxicity & is less myelosuppressive; although CTD is prothrombotic, overall VTE rates are no higher due to catheter-thrombosis with C-VAD.

CTD[2]

Cyclophosphamide 500mg PO once weekly
Thalidomide at 100mg and increasing to 200mg PO daily
Dexamethasone 40 mg PO daily on days 1-4 and 12-15
Cycles are repeated every 21 days

CTD disadvantages are primarily those of Thalidomide toxicity and include drowsiness, constipation, cumulative peripheral neuropathy, rash (occ. severe) and thromboembolism. Thalidomide is teratogenic & has specific pharmacovigilance accordingly. It can be given to patients with renal failure with little dose modification. Remissions should be consolidated with high dose therapy where possible (unconsolidated CTDa no better PFS/OS than M&P).

C-VAD

Cyclophosphamide 500mg O on days 1, 8 and 15
Vincristine 0.4 mg IV daily by continuous infusion for 4 days
Doxorubicin 9 mg/m^2 IV daily by continuous infusion over 4 days
Dexamethasone 40 mg PO daily on days 1-4
Cycles are repeated every 21 days
Delay course +/- G-CSF if neutrophils <1.0x10^9/l

Vincristine and doxorubicin should be infused together **via a central line** over 4 days using a pump or Baxter infuser. When disconnecting the pump, flush the line with normal saline before flushing with hep-flush (Heparin/Doxorubicin precipitate could form). C-VAD may be useful for patients with disease refractory to alkylating agents and can be given in renal failure without dose modification. Its disadvantages are the

need of central venous access, cardiotoxicity, neutropenia, line-infections and thrombosis. Remissions induced tend to be short lived (approximately 18 months) and hence the response should be consolidated with high dose therapy where possible.

Prophylaxis

Allopurinol 300 mg PO daily for the first 1-2 weeks
Proton pump inhibitors or H_2-antagonists with steroids
Fluconazole 50mg od PO daily with steroids
Aciclovir 400mg bd PO daily
Co-trimoxazole/other PCP prophylaxis as per local policy
Ondansetron/Metoclopramide/Cyclizine as required

Anti-thrombotic prophylaxis with LMWH, or dose-monitored full anticoagulation with warfarin is recommended for patients with >1 risk factor; vascular risk factors (previous DVT/PE, varicose veins, obesity, immobility etc), thalidomide/lenalidomide plus steroids, high plasma viscosity, high tumour burden, at induction. Alternatively low dose aspirin may be considered (Level 4 recommendation).

7.1.3 Stem cell mobilisation

Patients' should be referred early in their treatment (at 4th cycle of chemotherapy) to the transplant centres, allowing sufficient time for assessment and planning of stem cell mobilisation and high dose therapy. Patients' remission status & organ function should be assessed prior to harvest.

Peripheral blood stem cells are preferred to bone marrow because of faster recovery. Studies have shown that the bone marrow plasma cell percentage at time of peripheral blood stem cell collection does not correlate to outcome of high-dose therapy. Thus patients who have shown a response to chemotherapy should continue to stem cell collection, irrespective of plasma cell percentage. Even patients with chemo-refractory disease can achieve substantial remissions after high-dose therapy and can be referred for consideration, but newer treatments including Bortezomib mean that refractory disease is thankfully rare.

Various regimens exist for the mobilisation of peripheral blood stem cells. Most patients will have low levels of disease at this point, and priming chemotherapy with Cyclophosphamide 1.5-3.0g/m^2 plus Mesna and G-CSF can be given. Patients with significant residual disease may be considered for mobilisation with a regimen with anti-myeloma properties such as ESHAP or (V)DTPACE[3,4]. Those failing stem-cell

harvest can be considered for Plerixafor/GCSF mobilisation, which mobilises approx. 2/3 of those failing GCSF-alone (available at SCT centres, via IFR).

Apheresis should aim to harvest a target of $4x10^6$ $CD34^+$/kg (minimum of $2x10^6$ $CD34^+$/kg). If the patient may potentially be suitable for a second autologous transplant, enough stem cells for both procedures should be harvested at first response.

7.1.4 Off trial - Patients >70 years and NOT suitable for stem cell transplantation

Treatment of myeloma in the elderly should be tailored according to their age and co-morbidities. For many decades Melphalan and Prednisolone was the treatment of choice in this group of patients. Partial responses are seen in approximately 50% of patients. The Melphalan dose should be gradually escalated until the dose used causes moderate cytopenias. Response is gradual and most patients reach a stable plateau phase which lasts 12 -18 months before relapse.

Thalidomide-containing three drug combination regimens have, more recently, become the standard of care. These regimens, however, must be used with caution in frail patients due to their significant side effect profile. Best published evidence currently available for this group of patients exists for MPT (Melphalan, Prednisolone and Thalidomide). Whilst 4 randomised trials have shown higher response rates and longer DFS in the MPT group when compared to MP alone, OS was not uniformly prolonged. Two French trials using intensive MPT regimens have observed a significantly improved OS for patients treated with MPT over MP, including in >75 years[5] An Italian trial using a less intensive MPT failed to confirm higher OS, despite improved PFS; there was an unusually high OS for patients randomised to MP alone, as most subsequently received thalidomide due to poor initial response[6,7]. Although there is less published data available for the use of attenuated CTD, many clinicians have become familiar with this regimen; recent analysis from Myeloma IX trial does not however show improved DFS or OS despite greater response rates than MP[8].

The highest response rates (>70% PR & 30% CR), leading to progression-free & overall survival benefit, in this patient group have been achieved with VMP, a bortezomib-containing regimen. VMP may also be more effective in poor risk cytogenetics such as t(4;14)[9]. Bortezomib can cause significant neurotoxicity, & quality-of-life may be lower mid treatment on VMP; prompt dose-reduction &/or cessation is imperative during bortezomib treatment if emergent neuropathy. Bortezomib can also cause exacerbation of cytopaenia, gut disturbance & zoster. Although licensed for 1st line treatment, NICE guidance (2011) for induction is that

bortezomib-based induction in non-intensive patients is recommended only for those unsuitable for thalidomide (e.g. significant bradycardia, VTE-risk, & thalidomide-intolerance).

Bendamustine is an intravenous substituted alkylator with cell-cycle-regulatory effects; in phase III trial bendamustine was more effective in producing CR than MP & led to improved quality of life, but caused more cytopaenia[10]; NorthWestCDF have approved Bendamustine for 1st-line usage in myeloma patients not suitable for autograft. Bendamustine can be delivered even in significant renal impairment (eGFR>10ml/min), & is non-neurotoxic; it may be better option than MP for those who cannot receive thalidomide nor bortezomib-containing induction (e.g. pre-existing neuropathy).

Treatment choice remains the discretion of the treating physician, and should be tailored to the patients' physical state and co-morbidities. MRCIX data show those with very poor performance status/severe comorbidities do badly on CTDa, whereas good performance patients without adverse cytogenetics can expect good tolerability, response & remission duration. Caution re high-dose steroids (Pred & especially Dex) in elderly or frail.

MPT[5]
Melphalan 0.18mg/kg PO for 4 days
Prednisolone 2mg/kg PO for 4 days
Thalidomide initially at 50mg, increasing up to 200mg daily
Twelve cycles MP are repeated every 6 weeks

VMP[8]
Bortezomib 1.3mg/m^2 SC/IV days 1, 4, 8, 11, 22, 25, 29 & 32 for cycles 1-4; subsequent 5 cycles days 1, 8, 22 & 29
Melphalan 9mg/m^2 PO for 4 days
Prednisolone 60mg/m^2 PO for 4 days
First 4 cycles VMP are repeated every 6 weeks, latter 5 cycles every 5 weeks.

If the platelet count falls to <50x10^9/l or neutrophils <1.0x10^9/l melphalan should be reduced in subsequent courses to 6mg/m^2 (then 4.5mg/m^2), and consider GCSF for latter. Reduce dose of melphalan in elderly patients and those with renal impairment.

MP
Melphalan 9mg/m^2 PO for 4 days
Prednisolone 30-60mg/m^2 PO for 4 days
Cycles are repeated every 4-6 weeks (until plateau)

The neutrophil count should be ≥1.0x10^9/l and platelet count ≥75x10^9/l before treatment. In the first two cycles of treatment, neutrophil and platelet counts should be checked 21 days from the first melphalan in each cycle. If the platelet count falls to

<$75x10^9$/l or neutrophils <$1.0x10^9$/l melphalan should be reduced in subsequent courses to 3 or 4 days and consider GCSF. Reduce dose of melphalan in elderly patients and those with renal impairment.

CTDa[8] Cyclophosphamide 500mg once weekly
Thalidomide initially 50mg nocte, increasing up to 200mg
Dexamethasone 20 mg am on days 1-4 and 15-18
Cycles are repeated every 28 days

Weekly Cyclo/Dex Cyclophosphamide 200-400mg/m^2 weekly (or 50-100mg/day)
Dexamethasone 20mg am weekly or days 1-4, 15-18

This is a useful regimen for patients in the any of the following circumstances:

- neutrophil count is < 1.0 x 10^9/l and platelets < 75 x 10^9/l before induction treatment
- significant myelotoxicity with melphalan
- severe or dialysis dependant renal failure

BendamustinePred Bendamustine 150mg/m2 IV days 1 & 2
Prednisolone 60mg.m2 days 1-4
Cycles repeated every 4 weeks.

Z-Dex Idarubicin 40mg/m^2 PO divided over 4 days
Dexamethasone 40 mg daily on days 1-4, 8-11 and 15-18 first cycle, followed by days 1-4 only in subsequent cycles
Cycles are repeated every 21 days.

On the basis of a phase II trial the regimen may offer an alternative to VAD. However, there are no data on long-term outcome and remissions appear short unless consolidated (similar to VAD). Idarubicin causes alopecia, nausea, cytopaenia & cardiotoxicity.

Prophylaxis See under section 7.1.2

7.1.5 Patients in Severe Renal Failure

A proportion of myeloma patients present with severe renal failure (creatinine clearance <30ml/min). Regaining renal function is of paramount importance and patients should be given high-dose dexamethasone as soon as diagnosis is suspected/confirmed. CTD (or C-VAD) may be used, but alkylators may require dose

adjustment. Thalidomide appears deliverable in full dose despite renal failure. Bendamustine is deliverable in renal impairment, down to eGFR 10ml/min.

Recent data using bortezomib-containing combinations (VelDex, BCD, PAD) in patients with severe renal failure demonstrate high rates of rapid recovery of renal function and should be considered in those patients fit for treatment[9,11,12]. Velcade is now listed on NorthWest Cancer Drugs Fund for presentation in severe renal failure (nwcancerdrugsfund.org). EuLite study examines role rapid light-chain removal in addition to PAD induction in newly presenting patients with severe renal impairment (Creat>500) & is open at MRI (2012).

7.1.6 **AL Amyloidosis**

As response to Bortezomib-based regimens appears more rapid & deep than other induction in retrospective series, such regimens are often recommended by the National Amyloid Centre at Royal Free Hospital in London; provided NAC assessed, bortezomib for such patients at induction is NorthWest CDF approved. There is also NAC-led 1st/2nd-line RCT of BCD versus PAD open 2012.

7.1.17 **Plasma Cell Leukaemia**

This rare presentation with circulating plasma cells (2x10^9 per ml, or 20% PBMC) is also known as Myeloma with Peripheral Blood Involvement, & is high-risk feature (although secondary PCL at relapse even worse prognosis). Organs including liver & spleen may be involved. Consensus is that bortexomib-based regimens (e.g. PAD in younger/fitter patients, & BCD/VMP in elderly/unfit patients) may be treatment of choice, but there is no RCT data.

7.2 Second Line Chemotherapy

7.2.1 Patients refractory to first line chemotherapy and SCT-eligible

There is evidence that high dose therapy and autologous stem cell transplantation can induce remissions (including CR) in patients who are resistant to induction chemotherapy. The aim in these patients should therefore be to use second-line therapy that still allows peripheral blood stem cell collection and does not exclude them from proceeding to high-dose therapy.

As second line therapy a cisplatin-based regimen, such as ESHAP or DTPACE, may be given[3,4]. Both of these can be also used for stem cell mobilisation; give daily G-CSF from day +1 until stem cell harvest. Velcade-based regimens (see below) incl.VelDex,

BCD, PAD & VDTPACE are suitable for salvage in induction-failure & permit stem cell harvest. Second-line Velcade therapy is covered by NICE guidance (2007).

Failing to achieve a response, patients may proceed directly to autologous stem cell transplantation, or an alternative chemotherapy (e.g. lenalidomide-based) may be used prior to transplantation. Please discuss these cases with a transplant physician at an early time point, esp as prolonged Lenalidomide may impair harvest.

7.2.2 Patients refractory to first line chemotherapy and SCT-ineligible

If suitable for Bortezomib-containing regimen (see 7.2.3), NICE guidance suggests optimal cost-efficacy at 2nd line therapy; VMP or BCD are likely to induce high response rates, whilst VelDex may cause less cytopaenia in those with poor marrow reserve. In thalidomide-naïve consider MPT/CTDa. If neuropathy precludes the use of Thalidomide or Bortezomib, consider Lenalidomide (NWCDF approved).

BCD[13]	Bortezomib 1.3mg/m^2 SC/IV on days 1, 4, 8 and 11 Cyclophosphamide 500mg PO/week (MRCXI) or 50mg/day Dexamethasone 20mg PO on days 1-2, 4-5, 8-9, 11-12 Cycles repeated every 21 days (maximum 8)
VMP[9]	For protocol see section 7.1.4

7.2.3 Patients in first relapse

All patients with myeloma will eventually relapse, and should be considered for a clinical trial whenever possible. Suitability for subsequent high-dose therapy and stem cell rescue should be considered when re-treatment is being assessed. Patients who are fit for second high-dose chemotherapy with stem-cell support should not have stem-cell toxic reinduction therapy, unless already have adequate banked stem cell harvest. Second autograft alone is not advised for those less than 12 months after initial transplant.

Myeloma X – A multi-centre trial of relapse therapy for patients at least 18 months after 1st autologous stem cell transplant, with PAD (Bortezomib/Adriamycin/Dex) reinduction & responders randomised (provided stem cell harvest available) to 2nd autologous SCT vs 3 months weekly Cyclophosphamide maintenance. Currently open. Available at Christie & MRI.

Those patients not eligible for trial may be treated as per NICE recommendation using bortezomib at first relapse. Therefore all patients' suitability should be assessed and treatment considered within the Velcade Response Scheme (VRS), which gives reimbursement for non-responders (≤PR) after maximum 4 cycles.

Bortezomib is a proteosome inhibitor with multiple down-stream targets. Response to bortezomib monotherapy in relapsed myeloma is 43% PR+CR. The addition of dexamethasone is advised to potentiate response (www.bcshguidelines.com). Combination with adriamycin (PAD) or low-dose cyclophosphamide (BCD) increases response rate and kinetics with some potentiation of cytopaenias, and is not stem-cell toxic.[13,14,]

BD	Bortezomib 1.3mg/m^2 SC/IV days 1, 4, 8 and 11 Dexamethasone 20mg PO on days 1-2, 4-5, 8-9, 11-12 Cycles repeated every 21 days (maximum 8)
BCD[13]	For protocol see section 7.2.2
PAD[14]	Bortezomib 1.3mg/m^2 SC/IV on days 1, 4, 8 and 11 Adriamycin 9mg/m^2 IV on Days 1-4 Dexamethasone 40mg PO on days 1-4, 8-11 and 15-18 (reduce to D1-4 for cycles 2-4) 2-4 Cycles are repeated every 21 days

Bortezomib is neurotoxic and dose-reduction/schedule extension (as per SPC) is required in painful grade 1 or grade ≥2 neuropathy. Weekly administration appears to reduce neuropathy, as does subcutaneous delivery (recently licensed by this route); subcutaneous route is non-inferior for response, so recommended unless severe injection site reactions (usually manageable with topical steroid). Drug discontinuation may be necessary in more severe cases to prevent irreversible damage. Bortezomib also causes transient thrombocytopenia, which may need dose-reduction and/or platelet transfusion. Other toxicities include fatigue, GI-upset (esp. diarrhoea), vasculitic rash (sometimes steroid-responsive), postural hypotension and less frequently neutropenia/anaemia. Rarely liver, respiratory & cardiac dysfunction are described. Bortezomib potentiates viral infection esp VZV, so aciclovir prophylaxis advised even in monotherapy.

7. 3 Third (or higher) Line Chemotherapy

There is no uniformly established treatment for subsequent relapses and various options are available. Factors influencing treatment decisions include age, fitness/performance status, renal function, co-morbidities, depth and duration of response to prior treatment, tolerability of prior treatment and residual treatment toxicities such as neurotoxicity. In addition, quality of life should be considered whenever treatment is considered.

Reutilisation of previously effective chemotherapy is usually feasible and may produce further responses. Remission/plateau lasting at least 6-12 months would be desirable before reutilising a previous regimen. Otherwise change to agent(s) with alternative mode of action is suggested. For standard cytotoxics, response rates after first exposure are around 50-60%. There is less data for re-challenge with biological agents, although re-challenge with bortezomib has been shown to be feasible and potentially effective provided no significant residual neurotoxicity is observed (trial data suggest bortezomib re-treatment effective in over 50% of those who had at least PR with duration ≥6 months on first exposure). In principle, all prior listed chemotherapies may be used depending on the patients' co-morbidities and tolerabilities. Alternatively, please discuss with a myeloma consultant at one of the tertiary referral centres to enquire about ongoing phase I and II trials available.

The combination Lenalidomide plus Dexamethasone is NICE approved (2009) as third line therapy (or second line if bortezomib is contra-indicated e.g. in patients with neuropathy; NorthWestCDF approved). In two large randomised trials[15,16],. Len/Dex had an overall response rate of over 60% in patients with relapsed myeloma with a lower response in thalidomide-refractory patients (45% PR+CR). As the optimal treatment duration is unclear, and until further trial evidence is available, treatment is continued until response failure or significant toxicity occurs.

Len/High-Dose Dex Lenalidomide 25mg PO on D1-21
Dexamethasone 40mg PO on D1-4, 9-12 and 17-21 (reduce to D1-4 after 4 cycles)
Cycles are repeated every 28 days

Len/low dose dex Lenalidomide 25mg PO on D1-21
Dexamethasone 40mg PO once weekly
Cycles are repeated every 28 days

Lenalidomide causes neutropenia and thrombocytopenia which may require dose-interruption and reintroduction at lower doses (15mg, 10mg, 5mg sequentially), &/or GCSF support. Dose reduction is also required in renal impairment (Creatinine

clearance <50 ml/min). Other side effects are fatigue, infection and thromboembolism (requires VTE prophylaxis), as well as teratogenecity (requiring Celgene Prescription Authorisation Form). Monitoring of thyroid and liver function is advised. Lenalidomide is less neurotoxic than thalidomide, but often causes cramps, which may be responsive to magnesium &/or quinine. Although there is concern re secondary malignancies in maintenance Lenalidomide trials (esp. post autograft), this is not thought a significant issue with salvage Lenalidomide for relapsed/refractory disease. Although not directly stem-cell toxic, prolonged Lenalidomide can impair harvest, so if PBSCH is contemplated, mobilisation should occur before more than 6-8 cycles given.

8.0 STEM CELL TRANSPLANTATION

8.1 Allogeneic Myeloablative Stem Cell Transplant

This should be considered in patients <45 years of age with an HLA-identical sibling but may also be suitable for fit patients up to the age of 50. Whilst the treatment related mortality (TRM) is as high as 30-35%, studies have shown that 60% of patients undergoing myeloablative sibling conditioning in first response enter a CR with one-third remaining in long-term remission.

Matched unrelated full intensity transplants have an even higher TRM and are currently not routinely EBMT recommended; they can be considered for very young & very fit patients with high-risk disease (high stage/poor cytogenetics/plasmablastic or leukaemic disease).

8.2 Autologous Stem Cell Transplant

All fit patients not suitable for allogeneic myeloablative transplantation should be considered for high-dose Melphalan (200mg/m^2) and autologous stem cell rescue as part of their 1st line therapy. This is associated with complete remission rates varying between 50-60%, a low TRM (<2% in absence comorbidity) and a median survival of approximately 5-6 years. This procedure cannot be thought curative as most patients ultimately relapse. If the clinician is unsure as to the patient's suitability for high dose therapy we advise early discussion with a transplant physician at one of the regional transplant centres.

Patients relapsed >12 months following 1st autograft and fit can be considered for second autologous transplant. Second autograft is not advised for those relapsing

within 12 months of 1st autograft, and tandem autologous/allogeneic reduced intensity transplant can be considered, although non-curative & have high incidence GVHD/infections.

8.3 Allogeneic Non-Myeloablative Stem Cell Transplant

Non-myeloablative or reduced intensity conditioning transplants (RIC) are currently experimental, and the best conditioning regimen is not yet known. They allow older patients to receive a sibling or unrelated donor transplant with less toxicity and reduced TRM (10-15% at 3 months), but with risk GVHD & immunocompromise. 2 RCTs now suggest longer & deeper remissions with Seattle-conditioned tandem auto-allo approach with sibling donors (Bruno NEJM 2007; Gharton 2011). There is now NCRN LenaRIC trial available within the UK using T-depleted non-myelobalative regimen with early Lenalidomide. However, potential cases should be discussed directly with the transplant centres on an individual basis.

8.4 Tandem Stem Cell Transplant

Tandem (double) autografts have been shown to increase depth of remission after 1st high-dose chemotherapy in early trials[17] but benefit is largely confined to those not achieving very good partial remission following 1st autograft and may not lead to overall survival gain. Hence tandem autografts are not routinely recommended.

Recent reports of tandem autologous followed by RIC allograft suggest durable remissions in 40-60% of patients.[16] RIC transplant regimens involving substantial CAMPATH T-cell depletion are currently not recommended due to high rates of opportunistic infection and relapse.

8.5 Stem Cell Transplantation in Severe Renal Failure

High dose therapy (autologous and allogeneic transplantation) may also be considered for patients with severe renal impairment (creatinine clearance <30ml/min) but should only be carried out in a centre with special expertise and on-site dialysis unit. The TRM for patients with a creatinine clearance of 10-30ml/min and who are dialysis-independent is <4% whilst that in dialysis dependant renal failure (creatinine clearance <10ml/min) is reported in the order of 5-10%. High-dose therapy and stem cell rescue with or without dialysis are offered at Manchester Royal Infirmary in close collaboration with the renal team.

9.0 MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (MGUS)

Criteria for distinguishing myeloma from MGUS:

1. Plasma cell infiltration of bone marrow < 10%
2. No evidence of lytic lesions on plain x-rays
3. Low level paraprotein and/or light chains in serum and/or urine

The incidence of MGUS is uncommon below the age of 50 years and increases with advancing age. Lymphoproliferative disorders (LPD) such as CLL, low grade-NHL and Waldenströms must always be considered and excluded as a differential diagnosis.

Once the diagnosis is established, patients with MGUS should be followed up at 6-12 monthly intervals either by their GP or local haematologist. They should be assessed for signs of progression or transformation into myeloma, amyloidosis or another LPD. The Mayo clinic conducted a retrospective study looking at 1148 patients with MGUS and identified the risk of progression to myeloma can be stratified according to three risk factors: paraprotein other than IgG, paraprotein level >15g/L and abnormal sFLC.

No. of Risk Factors	**Risk of Progression at 20 years**
0	**5%** (2% when other causes of death are taken into account)
1	**21%**
2	**37%**
3	**58%**

The Mayo clinic therefore proposed that patients with no risk factors could be discharged to their GP without regular follow-up and advised to contact the haematology department if they develop symptoms suggestive of myeloma, LPD, amyloid and/or end-organ damage such as bone pain, anaemia, renal failure, hypercalcaemia, hyperviscosity syndrome or recurrent infections. All other patients should be followed up at 6 to 12 monthly intervals.

This may be considered on the discretion of the treating physician. However, further studies are required to validate the use of such risk stratification.

11. RADIOTHERAPY

Indications for referral:

1. Painful bony lesion(s) or troublesome extramedullary myelomatous deposit(s) not responding to systemic treatment. The treatment field should include the lesion with a margin of unaffected bone/tissue of at least 2cm. The whole bone does not need to be treated (to spare the bone marrow) but if close to the end of a long bone this should be included to facilitate field matching for future radiotherapy.
2. Cord or cauda equina compression due to myelomatous deposit. This is an emergency. Patients should be started immediately on steroids and the on-call Clinical Oncologist should be contacted via Christie Switchboard (0161-446 3000). An MR scan of the **whole** spine should have been performed to enable accurate localisation of all the disease to facilitate radiotherapy. Radiotherapy should be commenced within 24 hours. Very rarely radiotherapy can be omitted/delayed if the patient is asymptomatic or there has been a **complete** response to initial steroids where there may be a case for upfront chemotherapy. However, the case should still be discussed with the on call Clinical Oncologist. The treatment field should include the affected vertebrae(s) and at least one unaffected vertebrae above and below. Where possible the top and bottom of the field should be placed in the intervertebral space to allow for easy matching for future radiotherapy. The field should include the whole width of the vertebrae or lesion (whichever is widest) with a 1-2cm margin either side.
3. Post surgical stabilisation of myelomatous skeletal lesion. Radiation should be commenced within 2 weeks if possible and should cover all the prosthesis/pin with a 1-2cm margin.
4. Possible indication: Significant myelomatous lesion in a long bone even if asymptomatic where fracture is not imminent and so surgery is not indicated (or not possible) to prevent future fracture.
5. Dose 8-10Gy in 1 fraction, 20Gy/4-5 or 30Gy/8-10 which can usually be planned in the simulator. A higher dose can be used if there is a possibility of a solitary plasmacytoma (40-45Gy/20 or 50Gy/25) but this should be CT planned.

Radiation can be potentiated by a large number of systemic anti cancer treatments and so where possible these should be omitted during radiotherapy or

at least discussed with the treating Clinical Oncologist. Where the radiation field is likely to include lung, heart, kidney or neural tissue this is especially important. Particular care should be taken with anthracyclines, vincristine, bleomycin and gemcitabine as they are well known to be potent radiosensitisers. These drugs should never be given concurrently with radiotherapy and a 2 week 'wash out' period before and after radiation is recommended. Information about newer agents including bortezomib is sketchy and at present should be avoided during radiotherapy.

12. SOLITARY PLASMACYTOMA (Bone and extra-medullary)

Treatment of choice is localised radical radiotherapy. Once myeloma has been excluded and after discussion at the relevant MDT meeting the patient should be referred to Dr Maggie Harris, Clinical Oncologist (tel 0161-446 3302, fax 0161-446 8142). In emergency situations the on call clinical oncologist should be contacted via Christie switchboard (0161-446 3000). Radiotherapy treatment should be CT planned and the clinical target volume should be obtained from the gross tumour volume (GTV) with a 1-2cm margin. The subsequent planning target volume (PTV) will depend on set up error of the area treated. Dose to the PTV should be 40-45Gy/20 for lesions under 5cm. Lesions over 5cm appear to have a worse prognosis with increased local recurrence and should receive 50Gy/25 where possible. Response following radiotherapy may be slow (up to 6 months).

Close follow up to monitor for development of myeloma is important. In solitary bone PC radiotherapy gives a long term DFS in 30% of pts but the majority go onto develop multiple myeloma after a median of 2-4 years. Median overall survival is 7-12 years. For extramedullary PC the prognosis is better, with >90% local control for radiotherapy but 30-50% progress to myeloma after a median of 1.5.2.5 years (ref guidelines as above). Patients should therefore be seen 2-3 monthly for the first 3 years and 4-6 monthly thereafter and FBC, plasma viscosity, calcium, urea and electrolytes, serum and electrophoresis for BJP, serum immunoglobulins, serum free light chains and Beta 2 MG should be performed at each clinic visit. Repeat imaging of the lesion may be helpful in some cases. Relapsed/recurrent treatment is likely to be as myeloma but should involve discussion with the clinical oncologist.

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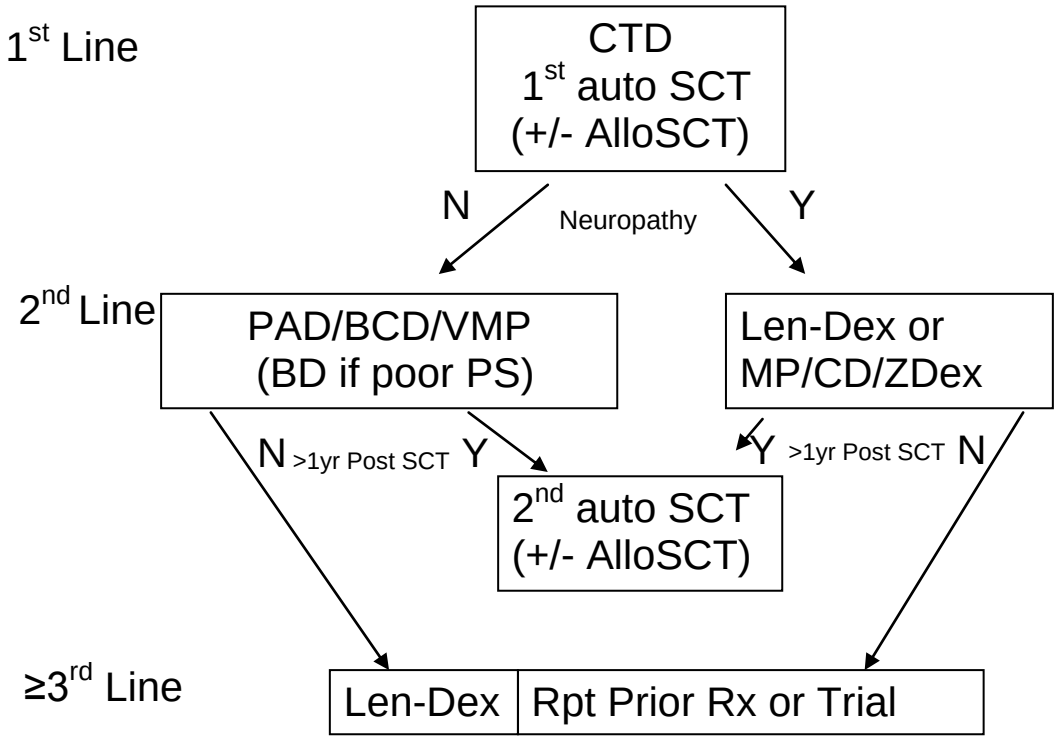
19. BCSH Guidelines (http://www.bcshguidelines.com)

14.0 APPENDICES

Examples of treatment: flow charts

A **<70yrs & No co-morbidities**



B **>70yrs &/or Co-morbidities**