

Protocol for Planning and Treatment

The process to be followed when a course of chemotherapy is required to treat:

MULTIPLE MYELOMA

Patient information given at each stage following agreed information pathway

1. DIAGNOSIS AND STAGING

Criteria for MGUS, Asymptomatic Myeloma and Symptomatic Myeloma

From the practical point of view, the key question is whether the patient needs treatment. For that reason, the International Myeloma Working group (2003) defined patient groups to identify those with MGUS, asymptomatic myeloma and symptomatic myeloma who require treatment:

MGUS

- M-protein in serum <30 g/L
- Bone marrow clonal plasma cells <10 %
- No myeloma-related organ damage or symptoms
- No other B-cell proliferative disorders amyloidosis etc

Asymptomatic Myeloma

- M-protein in serum >30 g/L AND/OR
- Bone marrow clonal plasma cells >10 %
- No myeloma-related organ damage or symptoms
- No other B-cell proliferative disorders amyloidosis etc

Symptomatic Myeloma

Bone marrow (clonal) plasma cells or biopsy proven plasmacytoma

- No specific level required for diagnosis. A small percentage of patients have no detectable M-protein in serum or urine but do have myeloma-related organ impairment and increased bone marrow plasma cells (non-secretory myeloma)

With signs or symptoms of

Myeloma-related organ Damage (*including bone lesions see below*)

- Patients without symptoms but with significant myeloma-related organ damage are grouped with symptomatic myeloma because of the need for treatment

Myeloma-Related Organ or Tissue Impairment (ROTI)*

(International Myeloma Working Group, 2003)

Clinical effects due to myeloma

- i) Increased calcium levels
Corrected serum calcium >0.25mmol/l above the upper limit of normal or >2.75mmol/l
- ii) Renal insufficiency
Attributable to myeloma

This document is uncontrolled when printed

File Name: LK-07	Page 1 of 9	Date of Issue: June 2011 Review Date: June 2013
Issue No.: 01/11	Written by: Dr D Gowans/ Dr G Marron	Authorised by: OHMMG

Clinical Management Protocol – Chemotherapy – Multiple Myeloma

- iii) Anaemia
Haemoglobin 2 g/dl (1.2 mmol/l) below the lower limit of normal or haemoglobin <10 g/dl (<100 g/L or 6.2 mmol/l)
- iv) Bone lesions
Lytic lesions or osteoporosis with compression fractures (this can be difficult in older patients where concomitant MGUS and osteoporosis may be more common)
(MRI or CT and bone marrow examination be required to clarify)
- v) Other
Symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (> 2 episodes in 12 months)

***Where there is uncertainty as to whether or not organ or tissue impairment is attributable to myeloma the percentage bone marrow plasma cells should be >30%**

2. TREATMENT OPTIONS

Asymptomatic Myeloma

Initial management - observation until disease progression.
Patients without clinical symptoms but with evidence of bone disease should commence treatment.

Symptomatic newly diagnosed

The current UK phase III study for newly diagnosed patients (Myeloma XI) is now open and should be considered for these patients.

Outwith the study treatment can be divided into intensive therapy for younger fitter patients and includes an autologous PBSC transplant procedure after cytoreductive therapy, or non-intensive therapy for other patients.

3. CHEMOTHERAPY

Intensive therapy

Generally considered for <65yrs
May be performed in older fitter patients.
May not be appropriate if <65 with significant comorbidities.

Cytoreductive therapy

Consider suitability for Myeloma XI clinical trial.
CTD or CVAD
High dose Dexamethasone may be used as initial therapy.

Choice of regimen at clinician's discretion depending on clinical circumstances.

Once plateau achieved (and patient achieved PR or CR) PBSC mobilisation with IV cyclophosphamide 1.5-3g/m² plus G-CSF.

Plerixifor can be considered in those who fail to mobilise with this approach.

This document is uncontrolled when printed

File Name: LK-07	Page 2 of 9	Date of Issue: June 2011 Review Date: June 2013
Issue No.: 01/11	Written by: Dr D Gowans/ Dr G Marron	Authorised by: OHMMG

Clinical Management Protocol – Chemotherapy – Multiple Myeloma

Patients failing to achieve PR should be considered on case-by-case basis. May benefit from autograft or second line therapy (see below)

Aim to collect $>2 \times 10^6$ cells/kg CD34/45 + cells at PBSC harvest.

Conditioning for autograft with Melphalan 200mg/m² with dose reduced to 140mg/m² in individuals with creatinine clearance 30-50ml/min and consider further dose reduction in severe renal impairment (creatinine clearance <30 ml/min) at clinicians discretion

HDT can be undertaken on patients with chronic renal impairment who are dialysis-dependent but only with very close liaison with the renal team in a highly selected group of patients. Melphalan should be administered 24 hours prior to dialysis with stem cells reinfused post-dialysis.

Allogeneic Stem Cell Transplantation

Myeloablative allogeneic stem cell transport may be considered in younger patients after discussion with the regional transplant centre. Current advice is to perform this in first plateau without prior autologous transplantation. Reduced intensity conditioning allogeneic transplantation should currently only be performed as part of a study protocol.

Non-intensive therapy

First line therapy in those felt appropriate for chemotherapy depends on clinical circumstances. Consider suitability for non-intensive arm of Myeloma XI clinical trial.

Outwith the study initial therapy with a thalidomide containing schedule such as CTDa or MPT would be considered standard but in older frailer patients alternatives such as MP should be considered. Palliative radiotherapy considered where appropriate either with or without chemotherapy.

Alternative treatments such as orthopaedic intervention (fixation) or vertebroplasty/kyphoplasty may be appropriate in selected individuals and this also applies to patients being treated intensively.

This document is uncontrolled when printed

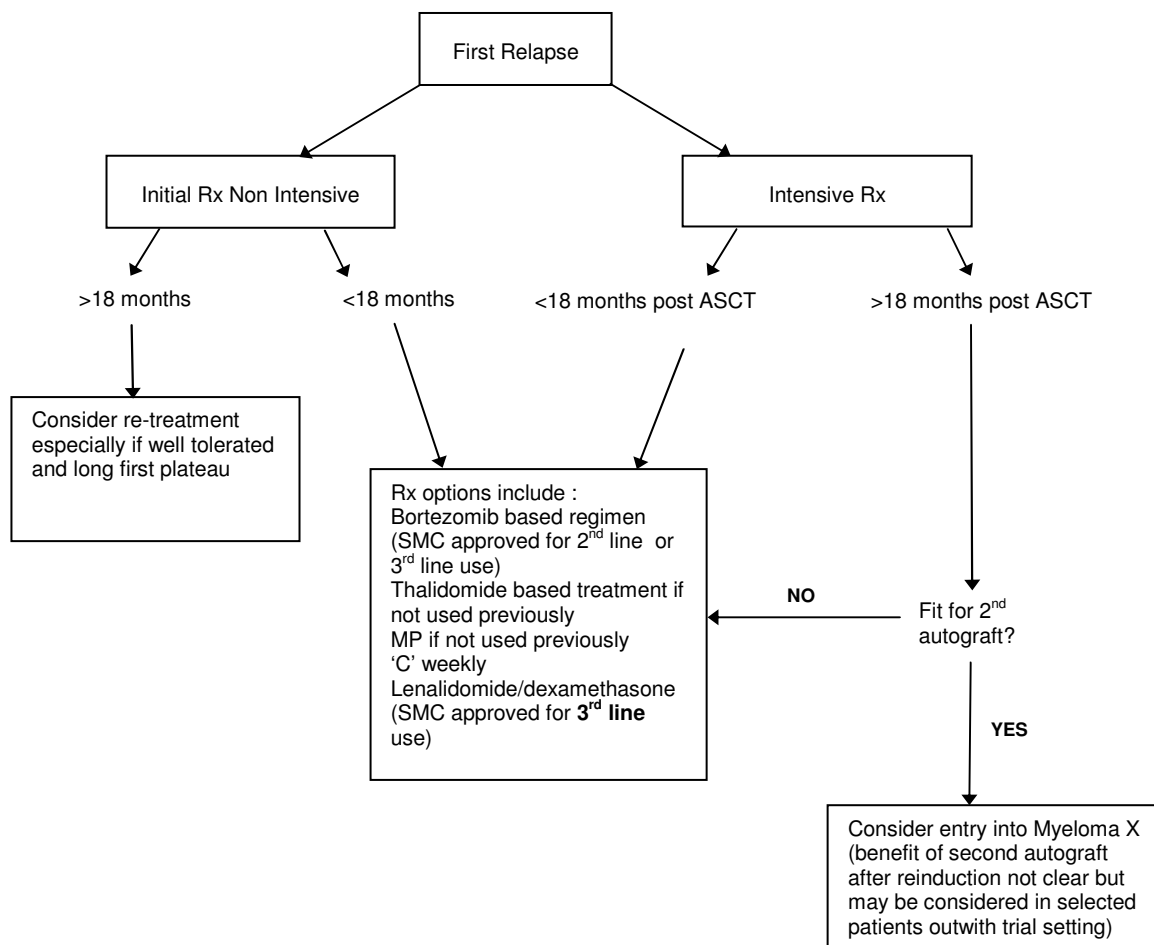
File Name: LK-07	Page 3 of 9	Date of Issue: June 2011 Review Date: June 2013
Issue No.: 01/11	Written by: Dr D Gowans/ Dr G Marron	Authorised by: OHMMG

Clinical Management Protocol – Chemotherapy – Multiple Myeloma

Relapsed Disease

Management of relapsed disease depends on

- Duration of response
- Prior therapy
- Relapse on treatment



This document is uncontrolled when printed

File Name: LK-07	Page 4 of 9	Date of Issue: June 2011 Review Date: June 2013
Issue No.: 01/11	Written by: Dr D Gowans/ Dr G Marron	Authorised by: OHMMG

Second or Later Relapse

The most appropriate management will be dependent on the individual's age, performance status, prior therapies, and response to these including previous toxicities. Therapeutic options include retreatment with previously effective regimens, or a different regimen (see diagram above for options). In addition other regimens, including intermediate-dose melphalan, thalidomide monotherapy and hemi-body radiotherapy (for extensive bone disease – see below) have been used in this setting and can prove effective but there are little data to support the optimal treatment at this stage of disease. Novel combinations of newer agents and established therapies have been used and show promise (such as PAD) with high response rates. None have shown survival advantage however but these approaches may be considered in difficult cases.

Lenalidomide is approved for third line use with dexamethasone. Given the myelosuppressive nature of this treatment and high doses of dexamethasone given, caution must be used in the elderly where it may not be appropriate and dose reduction of both lenalidomide and dexamethasone should be considered. Lenalidomide also requires dose modification in the presence of renal impairment.

Supportive Therapy

Treatment of Bone Disease

All patients receiving chemotherapy should receive a bisphosphonate. Their role in asymptomatic myeloma is less clear and may be guided by likelihood of progression to symptomatic MM and patient co-morbidities.

- Clodronate, pamidronate and zoledronic acid are all beneficial in Myeloma.
- Preliminary data from the Myeloma IX trial has indicated a potential survival advantage for zoledronic acid over clodronate. The benefit appears to be greatest in the first year of treatment. However there is no head to head data available comparing zoledronic acid with pamidronate, and therefore the choice of therapy should be determined by physician and patient preference. It is suggested that either pamidronate or zoledronic acid be used as initial therapy where possible whilst a patient has active disease, with clodronate being an option for longer term bone protection.
- Zoledronic acid may be preferred in the presence of progressive bone disease or refractory hypercalcaemia.
- Long term use of Zoledronic acid (and to a lesser extent pamidronate) is associated with a risk of osteonecrosis of the jaw.
- Evidence suggests no additional benefit of 90mg over 30mg pamidronate. There may be a lower risk of adverse events with 30mg. This dose is recommended unless patient circumstances indicate otherwise (e.g. refractory hypercalcaemia with renal impairment)
- All patients should be appropriately counselled and ideally have dental work performed before commencing long-term therapy. There should be close liaison with dental professionals in the event of dental problems whilst on bisphosphonates.
- Oral calcium 500mg and 400IU Vitamin D should be given with Zoledronic acid. There are no data for pamidronate and clodronate. Calcium supplementation might in fact impair clodronate absorption.

This document is uncontrolled when printed

File Name: LK-07	Page 5 of 9	Date of Issue: June 2011 Review Date: June 2013
Issue No.: 01/11	Written by: Dr D Gowans/ Dr G Marron	Authorised by: OHMMG

Clinical Management Protocol – Chemotherapy – Multiple Myeloma

In patients with renal impairment:

- Clodronate: half dose if creatinine clearance 10-30ml/min; contraindicated if <10ml/min.
- Pamidronate: reduce infusion rate to 20mg/hour if renal impairment.
- Zoledronic acid: check creatinine each infusion; contraindicated if creatinine > 265µmol/l, dose reductions apply depending on GFR.

-

Thromboprophylaxis

This should be considered in all patients, especially those receiving immunomodulatory drugs and those with a high burden of disease or other risk factors (e.g. immobility, recent orthopaedic/spinal Surgery). See also updated thalidomide SPC.

Management of Anaemia

Erythropoietin (EPO) is indicated for the treatment of anaemia in patients with Myeloma and chronic renal failure as per European guidelines for management of anaemia in patients with chronic renal failure.

At present, Transfusion support should be used to correct anaemia in individuals with normal renal function, EPO should only be considered in the context of recurrent transfusion reactions and EPO level < 200iu/ml.

Radiotherapy

Cord Compression – dexamethasone should be commenced immediately. Local radiotherapy is the treatment of choice and should be commenced as soon as possible, ideally within 24 hours of diagnosis.

Double hemi-body irradiation can be a useful palliative therapy in patients with widespread bone disease but can cause significant bone marrow suppression.

Symptomatic bone disease can be palliated with local radiotherapy but this may compromise bone strength. Cases considered on an individual basis after discussion with radiation oncology.

Solitary plasmacytomas should be considered for radiotherapy with curative intent.

Percutaneous Vertebroplasty/Balloon Kyphoplasty

May be indicated to provide pain relief in individuals with persistent severe painful osteoporosis with loss of height and/or compression fractures of the vertebral body.

Until further information available balloon kyphoplasty should only be considered within the context of a clinical trial.

4. TREATMENT DEFINITIONS

VAD

Vincristine 1.64mg IV Infusion over 96 hours

Doxorubicin 36mg/m² IV Infusion over 96 hours

Dexamethasone 40mg PO daily on Days 1 to 4 (and on days 8-11 in cycle 1 only)

Repeated every 3 weeks

This document is uncontrolled when printed

File Name: LK-07	Page 6 of 9	Date of Issue: June 2011 Review Date: June 2013
Issue No.: 01/11	Written by: Dr D Gowans/ Dr G Marron	Authorised by: OHMMG

Clinical Management Protocol – Chemotherapy – Multiple Myeloma

Melphalan /Prednisolone

Melphalan 7mg/m² oral Days 1-4 (round to nearest 2mg)

Prednisolone 40mg oral Days 1-4 (can be divided doses)

Repeated every 28 days continuing to a maximal response with a minimum of 6 courses and a maximum of 9 courses

CVAD

Cyclophosphamide 500mg PO daily on Days 1, 8 and 15

Vincristine 1.64mg IV Infusion Days 1 to 4

Doxorubicin 36mg/m² IV Infusion Days 1 to 4

Dexamethasone 40mg PO daily on Days 1 to 4 and on days 12 to 15

Repeated every 3 weeks (minimum of 4 cycles, maximum of 6 cycles)

ZDEX

Idarubicin 10mg/m² PO Daily on Days 1 to 4

Dexamethasone 40mg PO Daily on Days 1 to 4 (for cycle 1 only, also given on days 8-11 (4 days))

Repeated every 21 days

For multiple Myeloma (from WOS MM1 trial)

CYCLOPHOSPHAMIDE WEEKLY

Cyclophosphamide 300mg/m² PO Once Weekly

Prednisolone EC 40mg/m² PO Alternate Days for first 6 weeks only. Tail off over the next two weeks.

Repeated Weekly

IV CYCLOPHOSPHAMIDE

Cyclophosphamide 1.5 to 4g/m² IV Infusion Day 1

Single dose to mobilise stem cells

CTD (<65 years)

Cyclophosphamide 500mg PO Days 1, 8 and 15

Thalidomide 100mg Nocte for 1st 3 weeks then increased to 200mg Nocte thereafter

Dexamethasone 40mg Daily Days 1-4 and Days 12-15

Repeated every 21 days

For Myeloma

CTDa (>65 years)

Cyclophosphamide 500mg PO Days 1, 8, 15 and 22 (weekly)

Thalidomide 50mg Nocte for 1st 4 weeks increasing by 50mg increments to a maximum of 200mg Nocte at 4weekly intervals

Dexamethasone 20mg Daily Days 1-4 and Days 15-18

Repeated every 28 days

Maximum of 9 courses

This document is uncontrolled when printed

File Name: LK-07	Page 7 of 9	Date of Issue: June 2011 Review Date: June 2013
Issue No.: 01/11	Written by: Dr D Gowans/ Dr G Marron	Authorised by: OHMMG

BORTEZOMIB/DEXAMETHASONE

Bortezomib 1.3mg/m² IV Bolus Days 1, 4, 8 and 11

Repeated every 21 days

At least 72 hours should elapse between consecutive doses

Dexamethasone 20mg given on the day of and day after Bortezomib.

MTP

Melphalan 7mg/m² days 1-4

Prednisone 40mg days 1-4

Thalidomide 100mg

Repeat every 4 weeks for 6-9 cycles.

Lenalidomide /Dexamethasone

Lenalidomide 25mg daily for 21 days

Dexamethasone 40mg days 1-4, 9-12, 18-21 (see below re dose reductions)

Cycle repeats 28 days Dex reduced after 4 cycles. Treat till disease progression.

Lenalidomide dose reductions due to toxicity (principally myelosuppression) and renal function

Dexamethasone dosing:

The above schedule is the SMC approved and licensed dosing schedule but excess mortality has been observed in studies of older patients. Lower dose schedules such as those used in myeloma XI or weekly dosing should therefore be considered in these groups.

References

Desikan KR, Jagannath S, Siegel D (1996) Dexamethasone, cyclophosphamide etoposide and cisplatin (DCEP), an effective regimen for relapse after high-dose chemotherapy and autologous transplantation. *Blood* 88 (Suppl) : 2331a

Maclennan ICM, Chapman C, Dunn J, Kelly K (1992) Combined chemotherapy with ABCM vs. melphalan for treatment of myelomatosis. *Lancet* 339: 200

Dimopoulos MA, Kiamouris C, Moulopoulos LA. Solitary plasmacytoma of bone and extramedullary plasmacytoma. *Hematology-Oncology Clinics of North America* 1999; 13: 1249-1257.

Facon T, Mary JY, Hulin C et al (2007) *Lancet* 370:1209-18

Hulin C, Facon T, Rodon P et al (2009) Efficacy of Melphalan and Prednisone Plus Thalidomide in patients older than 75 years with newly diagnosed myeloma:IFM 01/01 trial.

Migliorati CA, Schubert MM, Peterson DE and Seneda LM (2005) Bisphosphonate-associated osteonecrosis of the mandibular and maxillary bone. *Cancer*, 104, 83-93.

Perry JJ, Fleming RA, Rocco MV, Petros WP, Bleyer AJ, Radford JE, Powell BL and Hurd DD. (1999) Administration and pharmacokinetics of high-dose cyclophosphamide with hemodialysis support for allogeneic bone marrow transplantation in acute leukaemia and end stage renal disease. *Bone Marrow Transplant*, 23, 839-842.

This document is uncontrolled when printed

File Name: LK-07	Page 8 of 9	Date of Issue: June 2011 Review Date: June 2013
Issue No.: 01/11	Written by: Dr D Gowans/ Dr G Marron	Authorised by: OHMMG

Clinical Management Protocol – Chemotherapy – Multiple Myeloma

Morgan GJ, Davies FE, Gregory WM et al (2010) First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial. Lancet 376(9757):1989-99

Palumbo A, Bringhen S, Caravita T et al (2006) Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised control trial. Lancet 367:825-31

Rajkumar SV, Fonseca R, Lacy MQ, Witzig TE, Lust JA, Greipp PR, Therneau TM, Kyle RA, Litzow MR, Gertz MA (1999) Autologous stem cell transplantation for relapsed and primary refractory myeloma. Bone Marrow Transplantation 23:1267

Rajkumar SV, Fonseca R, Dispenzieri A, Lacy MQ, Lust JA, Witzig TE, Kyle RA, Gertz MA, Greipp PR. 2000. Thalidomide in the treatment of relapsed multiple myeloma. Mayo Clin Proc 75:897-901

Richardson PG, Sonneveld P, Schuster MW, Irwin D et al (2005). Bortezomib or High Dose Dexamethasone for Relapsed Multiple Myeloma. N.Eng. J Medicine 352:2487-2498.

Author: Signature: Date:

Chair: Signature: Date:
(on behalf of OHMMG)

This document is uncontrolled when printed

File Name: LK-07	Page 9 of 9	Date of Issue: June 2011 Review Date: June 2013
Issue No.: 01/11	Written by: Dr D Gowans/ Dr G Marron	Authorised by: OHMMG