GUIDELINES FOR THE DIAGNOSIS AND MANAGEMENT OF MULTIPLE MYELOMA 2013

Jenny M. Bird[1], Roger G. Owen[2], Shirley D'Sa[3], John A. Snowden[4], Guy Pratt[5], John Ashcroft[6], Kwee Yong[7], Gordon Cook[8], Sylvia Feyler[9], Faith Davies[10], Gareth Morgan[11], Jamie Cavenagh[12], Eric Low[13], Judith Behrens[14] Matthew Jenner[15] **on behalf of the Haemato-oncology Task Force of the British Committee for Standards in Haematology (BCSH), UK Myeloma Forum**

Address for correspondence: Jenny Bird, c/o BCSH Secretary, British Society for Haematology, 100, White Lion Street, London, N1 9PF

e-mail: bcsh@b-s-h.org.uk

Correspondence prior to publication only:

Dr J M Bird
Avon Haematology Unit
Bristol Haematology and Oncology Centre
Horfield Road
BRISTOL
BS2 8ED

Tel: 0117 342 4394
Fax: 0117 342 4036
E-Mail: jenny.bird@uhbristol.nhs.uk

Acknowledgments

This guideline document was produced with the help of an educational grant from Myeloma UK.

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Annual review of recommendation updates will be undertaken and any altered recommendations posted on the websites of the British Committee for Standards in Haematology (http://www.bcshguidelines.com/) and UKMF (http://www.ukmf.org.uk/)

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1. Avon Haematology Unit, Bristol Haematology and Oncology Centre, Bristol
2. Department of Haematology, Leeds Teaching Hospitals NHS Trust
3. Department of Haematology, University College Hospital, London
4. Department of Haematology, Sheffield Teaching Hospitals NHS Trust
5. Department of Haematology, Heart of England NHS Trust, Birmingham
6. Department of Haematology, Leeds Teaching Hospitals NHS Trust
7. Department of Haematology, University College Hospital, London
8. Department of Haematology, Leeds Teaching Hospitals NHS Trust

9. Department of Haematology, Calderdale and Huddersfield NHS Trust
10. Haemato-oncology Unit, Royal Marsden Hospital, London
11. Haemato-oncology Unit, Royal Marsden Hospital, London
12. Department of Haematology, St. Bartholomew's Hospital, London
13. Myeloma UK, Edinburgh
14. Department of Haematology, St Helier Hospital, Carshalton, Surrey
15. Department of Haematology, University hospital Southampton

Key Words: myeloma, myeloma therapy, lymphoid malignancies, malignant haematology, laboratory haematology, immunoglobulin

This guideline is an update of the 2010 BCSH 'Diagnosis and management of multiple myeloma' guideline. It should be in conjunction with the BCSH guideline 'Supportive care in multiple myeloma'.

The contents of 'Diagnosis and management of multiple myeloma' are listed below:

The key areas that are covered comprehensively in the document entitled 'Guidelines for Supportive Care in Multiple Myeloma 2011' (Snowden et al 2011) are listed below:

- Anaemia
- Haemostasis and thrombosis issues
- Pain management
- Peripheral neuropathy
- Other symptom control – gastrointestinal, sedation/fatigue, mucositis
- Bisphosphonate-induced osteonecrosis of the jaw
- Complementary therapies
- End of life care

1. Methodology, epidemiology and clinical presentation

1.1 Methodology

The production of these guidelines involved the following steps:

- Establishment of working groups in the topic areas detailed above followed by review of key literature to April 2013 including Cochrane database, Medline, internet searches and major conference reports

- Development of key recommendations based on randomized, controlled trial evidence. In the absence of randomized data, recommendations were developed on the basis of literature review and
a consensus of expert opinion
- Involvement of patient advocacy through Myeloma UK
- Review by UK Myeloma Forum (UKMF) Executive and British Committee for Standards in Haematology (BCSH) Committees
- Review by a British Society for Haematology (BSH) sounding board

Levels of evidence and grades of recommendation have been updated using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) nomenclature for assessing the quality of evidence and providing strength of recommendations (http://www.gradeworkinggroup.org/index.htm). In preparing these guidelines the authors have considered overall cost-effectiveness of recommended interventions as well as clinical efficacy data but formal health economic assessments have not been carried out.

1.2 Incidence, prevalence and epidemiology

The annual incidence of myeloma in the UK is approximately 60-70 per million (http://info.cancerresearchuk.org/cancerstats/types/multiplemyeloma/incidence/index.htm). The overall prevalence is likely to be increasing given the recently published data demonstrating improved survival rates over the last decade (Brenner *et al,* 2009; Kumar *et al,* 2008a). The median age at presentation is approximately 70 years. Only 15% of patients are aged less than 60 years. Myeloma has a higher incidence in Afro-Caribbean ethnic groups than in Caucasians but there are few other distinctive epidemiological features. The majority of cases present *de novo* but it is now recognized that myeloma is preceded by an asymptomatic monoclonal gammopathy of undetermined significance (MGUS) phase in virtually all patients (Landgren *et al,* 2009).

1.3 Clinical Presentation

Presenting clinical features include symptoms of:

- Bone disease
- Impaired renal function
- Anaemia
- Hypercalcaemia
- Recurrent or persistent bacterial infection
- Hyperviscosity

Other patients are diagnosed following the incidental detection of a raised erythrocyte sedimentation rate (ESR), plasma viscosity, serum protein or globulin. Patients with suspected

myeloma require urgent specialist referral. Spinal cord compression, hypercalcaemia and renal failure are medical emergencies requiring immediate investigation and treatment. The investigation and management of asymptomatic patients found to have an M-protein are discussed in the UKMF/BCSH MGUS guidelines (Bird *et al,* 2009).

2. Diagnosis, prognostic factors and disease monitoring

2.1 Investigation and diagnosis

Investigation of a patient with suspected myeloma should include the screening tests indicated in Table 1, followed by further tests to confirm the diagnosis. Electrophoresis of serum and concentrated urine should be performed, followed by immunofixation to confirm and type any M-protein present. Immunofixation and serum-free light chain (SFLC) assessment are indicated in patients where there is a strong suspicion of myeloma but in whom routine serum protein electrophoresis is negative (Pratt 2008).

Quantification of serum M-protein should be performed by densitometry of the monoclonal peak on electrophoresis; immunochemical measurement of total immunoglobulin (Ig) isotype level can also be used and is particularly useful for IgA and IgD M-proteins. Quantification of urinary total protein and light chain excretion can be performed directly on a 24-h urine collection or calculated on a random urine sample in relation to the urine creatinine.

Quantification of SFLC levels and κ/λ ratio is an additional tool for the assessment of light chain production. The serum tests are particularly useful for diagnosis and monitoring of light chain only myeloma (Bradwell *et al,* 2003) and patients with oligosecretory / non-secretory disease (see Table 2) (Drayson *et al,* 2001) and in requests for which urine has not been sent to the laboratory. In renal impairment the half-life, and thus serum concentration of SFLC, can increase ten-fold and there is often an increased κ/λratio (Hutchison *et al,* 2008). A diagnosis of myeloma should be confirmed by bone marrow (BM) assessment. It is recommended that an adequate trephine biopsy of at least 20 mm in length be obtained in all patients as it provides a better assessment of the extent of marrow infiltration than aspirate smears (Al-Quran *et al,* 2007; Ng *et al,* 2006).

It is recommended that a diagnosis of myeloma be confirmed by the demonstration of an aberrant plasma cell phenotype and / or monoclonality. Plasma cell phenotyping may be performed by flow cytometry and / or immunohistochemistry on trephine sections. The European Myeloma Network have provided practical guidance on the optimal methods for flow cytometry (Rawstron *et al,* 2008) and rapid and cost effective single-tube assays have been developed (Rawstron *et al,* 2008). CD138 immunostaining of trephine sections can be useful to determine the extent of infiltration in selected cases (Al-Quran *et al,* 2007; Ng *et al,* 2006). All diagnoses should be made or reviewed by an appropriately constituted Multidisciplinary Team (MDT) (National Institute for Health and Clinical Excellence [NICE], 2003). Cytogenetic and radiological investigations are discussed in sections 2.4 and 3, respectively.

2.2 Diagnostic criteria and differential diagnosis

A diagnosis of myeloma should be made using the criteria proposed in 2003 by the International Myeloma Working Group (IMWG), which are detailed in Table 2.

These criteria distinguish between myeloma and MGUS principally on the basis of M-protein concentration, percentage of BM plasma cells and presence or absence of myeloma-related organ and tissue impairment (ROTI, Table 3). Other differential diagnoses in patients with M-proteins include solitary plasmacytoma and other B-cell lymphoproliferative disorders. Detailed guidance on the diagnosis and management of solitary plasmacytoma and MGUS are provided in recently published UKMF/BCSH guidelines (Hughes *et al,* 2009; Bird *et al,* 2009).

Recommendations (all Grade A1)

- IMWG diagnostic criteria should be used
- Investigation should be based on the tests shown in Table 1 including an assessment of possible myeloma-related organ and tissue impairment
- All diagnoses should be made or reviewed by an appropriately constituted MDT
- Plasma cell phenotyping by flow cytometry and / or immunohistochemistry on trephine biopsy sections is recommended in all cases

2.3 Monitoring and indications for starting therapy

Chemotherapy is indicated for the management of symptomatic myeloma defined by the presence of ROTI. Early intervention in patients with asymptomatic myeloma is not required (Hjorth *et al,* 1993; Riccardi *et al,* 2000) although chemotherapy may be considered in patients with a rising M-protein concentration in the absence of ROTI. Patients with asymptomatic myeloma require close monitoring under the supervision of a Consultant Haematologist.

The overall risk of progression is 10% per year for the first 5 years but, interestingly, declines in subsequent years (Kyle *et al,* 2007). The SFLC ratio ($\leq$0.125 or $\geq$8) appears to be predictive of outcome and a risk score incorporating BM plasma cell percentage, M-protein concentration and SFLC ratio has been proposed (Dispenzieri *et al,* 2008). Flow cytometry is also predictive of outcome as the risk of progression is significantly greater when aberrant phenotype plasma cells determined by flow cytometry comprise $\geq$95% of total BM plasma cells (Perez-Persona *et al,* 2007).

Recommendations

- Chemotherapy is only indicated in patients with symptomatic myeloma based on the presence of ROTI (Grade C2)

- Patients with asymptomatic myeloma should be monitored under the supervision of a Consultant Haematologist. These patients should be offered entry into clinical trials if available. (Grade A1)
- Monitoring of patients with asymptomatic myeloma should include regular (typically 3-monthly) clinical assessment for the emergence of ROTI and measurement of serum and urinary M-protein (and SFLC when indicated). Repeat BM examination and skeletal imaging should be considered prior to the start of treatment (Grade A1)

2.4 Prognostic factors and staging in symptomatic myeloma

The natural history of myeloma is heterogeneous with survival times ranging from a few weeks to >20 years. Analysis of prognostic factors is essential to compare outcomes within and between clinical trials. The Durie/Salmon staging system was published in 1975 (Durie and Salmon 1975) but has been superseded by the International Staging System (ISS) reproduced in Table 4 (Greipp*, et al* 2005). This defines 3 risk categories determined by the serum concentration of β2-microglobulin and albumin. The use of staging systems to determine choice of therapy for individual patients remains unproven.

Certain cytogenetic and molecular genetic abnormalities have been shown to predict outcome in myeloma. It is now generally accepted that both the immunoglobulin heavy chain gene translocations t(4;14), t(14;16) and t(14;20) as well as the copy number changes 1q gain and 17p deletion, demonstrated by fluorescence in situ hybridization (FISH), confer an adverse outcome in myeloma. It has therefore been proposed that these abnormalities define "high-risk" myeloma and should be specifically sought at diagnosis in all patients (Fonseca*, et al* 2009, Munshi*, et al* 2011). Recent data suggests that chromosome 13 deletion is not an independent prognostic marker and the adverse effect relates to its close association with high-risk abnormalities, particularly the t(4;14). There is now consensus that conventional karyotyping has little or no added value in the routine setting (Fonseca*, et al* 2009). The European Myeloma Network have outlined the technical aspects of FISH testing in myeloma and related disorders and recommended the essential abnormalities to be tested for are t(4;14), t(14;16) and 17p13 deletions as well as 1p and 1q abnormalities where possible (Ross*, et al* 2012).

Data from the MRC Myeloma IX trial has been used to define risk groups based on the presence or absence of multiple adverse FISH lesions and to combine these with the ISS. This is able to identify an ultra-high-risk group defined by ISS II or III and >1 adverse lesion, associated with a short PFS (Boyd*, et al* 2012). This information is helpful to inform clinical discussions with patients about anticipated longer term outcome. There is increasing data to suggest that the adverse effect of genetic factors may at least in part be overcome by newer agents (Avet-Loiseau*, et al* 2010,

Sonneveld, *et al* 2012) and some centres propose a treatment approach based on genetic risk stratification with an emphasis on bortezomib-based induction for high risk myeloma (Kumar, *et al* 2009). Whilst there is now international consensus about the need to undertake FISH analysis at diagnosis (Kyle and Rajkumar 2009) there is not yet international consensus as to the optimal treatment approach for different risk groups and further studies for high risk myeloma are required. Nonetheless using cytogenetics as a biological risk assessment is likely to assist in treatment decisions in the future as further evidence is generated about the optimal treatment for a given group of patients Next generation sequencing is able to identify copy number alternations, translocations and somatic mutations in myeloma cases (Chapman, *et al* 2011) and is likely to succeed FISH testing in the future.

A number of groups have used gene expression profiling to define risk in both newly diagnosed and relapsed patients (Shaughnessy, *et al* 2007) and DNA arrays to identify copy number abnormalities in newly diagnosed myeloma (Avet-Loiseau, *et al* 2009, Walker, *et al* 2010) but their role in determining treatment decisions in routine clinical practice is yet to be defined. Baseline SFLC concentration may also provide useful prognostic information (Dispenzieri, *et al* 2008) as may the immunoglobulin heavy/light chain ratios both at diagnosis and following treatment (Ludwig, *et al* 2010). The presence or absence of neoplastic plasma cells identified by multiparameter flow cytometry following treatment is also predicitive of long term outcome in both intensively and non-intensively treated patients (Paiva, *et al* 2012, Paiva, *et al* 2008). It is essential that new prognostic indicators continue to be evaluated in prospective clinical trials to determine the role for these in the future stratification of myeloma treatment.

Recommendations (all Grade C1)

- The International Staging System based on serum albumin and β2-microglobulin should be used
- FISH studies are recommended for all patients at diagnosis as they provide important prognostic information but their role in directing therapy needs further evaluation in prospective clinical trials
- Newer techniques for prognostic assessment should continue to be utilised in the context of clinical trials to evaluate future incorporation in to routine clinical practice.

2.5 Measuring Response to Therapy

The European Group for Blood and Bone Marrow Transplant / International Bone Marrow Transplant Registry / American Bone Marrow Transplant Registry (EBMT/IBMTR/ABMTR) criteria (Blade *et al,* 1998) were updated by the IMWG in 2006 (Durie *et al,* 2006) and further modifications

were subsequently proposed (Rajkumar & Kyle, 2009; Rajkumar *et al,* 2010). The uniform response criteria are detailed in Table 5.

There are two new response categories, stringent complete response (sCR) and very good partial response (VGPR). The criteria now incorporate changes in the SFLC assay but only for those patients with non-quantifiable serum or urine M-proteins defined as a serum M-protein of <10g/l and/ or urinary M-protein of <200 mg/24 h. In routine clinical practice there is a clear rationale for utilising the SFLC assay to assess response in light chain only disease, irrespective of the extent of light chain excretion in the urine (Pratt 2008). The response category 'sCR' (for use in the reporting of clinical trials) has been refined recently to incorporate the use of flow cytometry to detect minimal residual disease on the basis of the presence of an aberrant immunophenotype (Rajkumar *et al,* 2011). Low levels of residual disease may also be demonstrated using allele-specific polymerase chain reaction (PCR) and a further new category of molecular CR is proposed, which is defined as the absence of disease by sequence specific PCR methods with a sensitivity of 10^{-5}.

Delayed achievement of complete remission (CR) is seen in a significant proportion of patients following high-dose therapy (Davies *et al,* 2001). The majority of such patients will have IgG M-proteins which have a half-life of approximately 23 days, significantly longer than that of IgA (6 days) and free light chains (4 h) (Mead *et al,* 2004).

Repeat BM aspirate assessment is required to confirm CR (repeat trephine biopsy is not required under the response criteria but may be needed for accurate assessment) (Durie *et al,* 2006) and should be performed in all patients at Day 100 following high-dose therapy in accordance with EBMT standards. Flow cytometric assessment of minimal residual disease at this time point also provides prognostic information (Paiva *et al,* 2008) and may in the future be used to guide maintenance / consolidation therapies. The definitions of progressive disease and relapse have also been revised by the IMWG (table 6) and include a new category of clinical relapse, which reflects the fact that progressive disease (PD) as defined does not necessarily indicate a need for further therapy.

Note - in patients in whom the only measurable disease (for definitions see below) is by SFLC assay, CR is defined by negative immunofixation and a normal SFLC ratio, VGPR is defined by ≥90% decrease in the difference between the involved and uninvolved free light chain concentrations and PR by a ≥50% decrease in the difference between involved and uninvolved SFLC levels. If SFLC assay is also uninformative, PR is defined by >50% reduction in BM plasma cells provided baseline BM plasma cell percentage was ≥30%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required.

Definitions of measurable disease

Response criteria for all categories and subcategories of response except CR are applicable only to patients who have 'measurable' disease defined by at least one of the following three measurements:

- Serum M-protein > >10 g/l
- Urine M-protein >200 mg/24 h
- SFLC assay: Involved FLC level >>100 mg/l provided SFLC ratio is abnormal

Recommendations (all Grade B1)

- Response to therapy should be defined using the IMWG uniform response criteria
- The response category sCR is recommended only for use in the clinical trial setting
- The SFLC assay should be used to assess response in all patients with light chain only, non secretory and oligosecretory disease

2.6 Rare myelomas

The rare myelomas comprise up to 7% of all myelomas and consist of plasma cell leukaemia, IgD, IgE, IgM and non-secretory myeloma.

Plasma Cell Leukaemia

Plasma cell leukaemia (PCL) may be primary or secondary to multiple myeloma and is characterized by the presence of ≥20% circulating plasma cells and/or an absolute level of > 2.0 x 10^9/l (Kyle *et al,* 1974).

IgD, E and M Myelomas

IgD myeloma may comprise up to 1.8% of all myelomas (Blade and Kyle 1994; Wechalekar *et al,* 2005). Diagnosis may be difficult because some patients may present with a very small or no visible monoclonal spike on serum electrophoresis. Care must be exercised to avoid a false diagnosis of non-secretory or light chain only myeloma (Sinclair 2002).The clinical features are similar to that of other myelomas but Bence-Jones proteinuria, extramedullary involvement, lytic lesions and amyloidosis seem to be more frequent (Jancelewicz *et al,* 1975). Relatively few cases of IgE myeloma have been reported in the literature (Endo *et al,* 1981; Kairemo *et al,* 1999) Morris *et al,* in press). There may be clinical similarities with IgD myeloma and in both conditions the prognosis appears to be poor (Morris *et al,* in press). With the increased use of BM trephine biopsies and improved immunohistomorphology (Feyler *et al,* 2008; Konduri *et al,* 2005), IgM myelomas are being recognized more frequently and may comprise up to 0.4% of all myelomas (Morris *et al,* in press). It is important that such cases are distinguished from other IgM secreting disorders, particularly Waldenstrom macroglobulinaemia (Avet-Loiseau *et al,* 2003a). There is a high incidence of the t(11;14) and prognosis appears to be poor (Avet-Loiseau *et al,* 2003b; Feyler *et al,* 2008; Morris *et al,* in press).

Non-secretory myeloma

Non-secretory myeloma poses particular diagnostic difficulties as there is no serum M-protein and no urinary Bence-Jones protein excretion. The SFLC assay is informative in approximately two thirds of patients (Drayson *et al,* 2001). While the clinical presentation is essentially similar to standard myeloma, anaemia and lytic lesions may be seen more frequently while renal failure is uncommon (Morris *et al,* in press).

3 Imaging techniques

Significant advances in available imaging technologies have paralleled developments in therapy for myeloma and may play a more prominent role in determining prognosis in the future (Durie 2006). A detailed guideline for the use of imaging in myeloma has been published (D'Sa *et al,* 2007). Key recommendations are summarized below.

Recommendations

- The skeletal survey remains the screening technique of choice at diagnosis. (Grade B1)
- The skeletal survey should include a postero-anterior (PA) view of the chest, antero-posterior (AP) and lateral views of the cervical spine, thoracic spine, lumbar spine, humeri and femora, AP and lateral view of the skull and AP view of the pelvis; other symptomatic areas should be specifically visualized with appropriate views (Grade B1)
- Computerized tomography (CT) scanning or magnetic resonance imaging (MRI) should be used to clarify the significance of ambiguous plain radiographic findings, such as equivocal lytic lesions, especially in parts of the skeleton that are difficult to visualize on plain radiographs, such as ribs, sternum and scapulae (Grade A1)
- Urgent MRI is the diagnostic procedure of choice to assess suspected cord compression in myeloma patients with or without vertebral collapse. Urgent CT scanning is an alternative, when MRI is unavailable, intolerable or contraindicated.
- CT or MRI is indicated to delineate the nature and extent of soft tissue masses and where appropriate, tissue biopsy may be guided by CT scanning (Grade A1)
- There is insufficient evidence to recommend the routine use of positron-emission tomography (PET) or ^{99m}Technetium sestamibi (MIBI) imaging. Either technique may be useful in selected cases for clarification of previous imaging findings preferably within the context of a clinical trial (Grade C2)
- Bone scintigraphy has no place in the routine staging of myeloma (Grade A1)
- Routine assessment of bone mineral density cannot be recommended, owing to the methodological difficulties of the technique and the universal use of bisphosphonates in all symptomatic myeloma patients (Grade A1).

4 Management of common medical emergencies in myeloma patients

4.1 Hyperviscosity

Hyperviscosity syndrome may develop in patients with high serum paraprotein levels, particularly those of IgA and IgG3 type. Symptoms include blurred vision, headaches, mucosal bleeding and dyspnoea due to heart failure.
All patients with high protein levels should undergo fundoscopy, which may demonstrate retinal vein distension, haemorrhages and papilloedema. Patients usually have raised plasma viscosity and symptoms commonly appear when it exceeds 4 or 5 mPa. This usually corresponds to a serum IgM level of at least 30 g/l, an IgA level of 40 g/l and an IgG level of 60 g/l (Mehta and Singhal 2003). Plasma viscosity results should not be used to determine the need for plasma exchange as this may result in delay but testing should be carried out both before and after the procedure. Symptomatic patients should be treated urgently with plasma exchange; isovolaemic venesection may be useful if plasma exchange facilities are not immediately available. If transfusion is essential, exchange transfusion should be performed. The need for further exchanges over the next few days should be determined by symptoms and requirement for blood transfusion. Rapid reduction of protein levels is mandatory and anti-myeloma treatment should be instituted promptly.

Recommendations

- Symptomatic hyperviscosity should be treated with therapeutic plasma exchange with saline fluid replacement (Grade A1)
- If plasmapheresis is not immediately available but hyperviscosity symptoms are present, consider isovolaemic venesection with saline replacement as a holding measure (Grade A1)
- Effective treatment of the underlying disease should be started as soon as possible (Grade A1)

4.2 Hypercalcaemia

Up to 30% of myeloma patients present with hypercalcaemia occurring mostly in the context of active disease. Acute hypercalcaemia can present with central nervous system dysfunction (confusion, coma and obtundation), muscle weakness, pancreatitis, constipation, thirst, polyuria, shortening of the Q-T interval on electrocardiogram and acute renal insufficiency. Alternative causes of hypercalcaemia should be considered eg. hyperparathyroidism. Treatment of the underlying disease should be initiated as soon as possible along with active treatment of hypercalcaemia to minimize long-term renal damage. The mainstays of treatment are hydration and intravenous bisphosphonates.

Mild hypercalcaemia (corrected calcium 2.6-2.9 mmol/l) may be corrected with oral and/or intravenous rehydration. Moderate to severe hypercalcaemia (corrected calcium ≥ 2.9mmol/l) requires intravenous rehydration with normal saline. Adequate urine output should be ensured and use of intravenous loop diuretics, such as furosemide, should be considered to avoid volume overload and heart failure and promote urinary calcium excretion.

All patients with moderate to severe hypercalcaemia should receive a bisphosphonate. A randomized controlled trial in patients with hypercalcaemia of malignancy has shown that zoledronic acid is superior to pamidronate (Major *et al,* 2001). If the calcium remains high after 72 h a further dose of zoledronic acid may be given. Dose modifications are required in renal impairment and reduced dose pamidronate (30mg) may be more appropriate in patients with severe renal impairment (see Appendix 2). Patients with refractory hypercalcaemia may require corticosteroids and calcitonin.

Recommendations (mostly grade C; level III evidence)

- in mild hypercalcaemia (corrected calcium 2.6-2.9 mmol/l) re-hydrate with oral and /or iv fluids (Grade A1)
- in moderate-severe hypercalcaemia (corrected calcium >2.9 mmol/l) re-hydrate with intravenous fluids and give furosemide if required (Grade B1)
- zoledronic acid is the bisphosphonate of choice in the treatment of hypercalcaemia (Grade B1)

4.3 Cord compression

Compression of the spinal cord from extramedullary foci of disease occurs in 5% of patients with myeloma during the course of their disease (Kyle *et al,* 2003). Clinical features depend on the nature of the cord compression (due to bony / structural lesion or to soft tissue disease), the spinal level, extent of disease and the rate of development of cord compression, but commonly include sensory loss, paraesthesiae, limb weakness, walking difficulty and sphincter disturbance. This is a medical emergency requiring rapid diagnosis and treatment. Upon clinical suspicion of cord compression, dexamethasone 40 mg daily for 4 days should be commenced and MRI obtained as soon as possible. Where MRI is unavailable or impossible due to patient intolerance or contraindication, an urgent CT scan should be performed. The differentiation between soft tissue and bone-related cord compression is essential and should be discussed with neurosurgery/orthopaedic teams (depending on local expertise) immediately if there is any question about the need for surgical intervention.

Surgery is usually undertaken for emergency decompression in the setting of structural compression and/or to stabilize the spine and is usually consolidated by post-operative radiotherapy. For soft tissue disease local radiotherapy is the treatment of choice and should be commenced urgently, preferably within 24 hours of the diagnosis of cord compression. There are no randomized controlled trials to give guidance on optimal radiotherapy dose and fractionation but a retrospective multi-centre study of 172 myeloma patients has been published and demonstrated a better overall outcome in terms of improvement in motor function for patients treated with at least 30 Gy (Rades *et al,* 2006).

Recommendations

- Urgent MRI should be performed and neurosurgical or spinal surgical / clinical oncology consultation obtained (Grade A1)

- Local radiotherapy is the treatment of choice for non-bony lesions and should be commenced as soon as is possible, preferably within 24 h of diagnosis. A dose of 30 Gy in 10 fractions is recommended (Grade B1)

- Surgery is recommended for emergency decompression in the setting of bony compression and/or to stabilize the spine (Grade A1)

- If cord compression is a presenting symptom, it is important to concurrently pursue a rapid diagnosis and to institute systemic therapy as soon as possible (Grade A1)

4.4 Early Infection

Myeloma is associated with an increased incidence of early infection. This is related to deficits in both humoral and cellular immunity, reduced mobility and performance status, which are all associated with both the disease and its treatment. It has been reported that up to 10% of patients die of infective causes within 60 days of diagnosis (Augustson *et al,* 2005). Neutropenia is not usually a factor in early infection (Augustson *et al,* 2005)

There is increasing evidence showing that high dose steroids in the elderly or in patients with poor performance may be detrimental, with increased toxicity and a higher mortality rate in the short-term, and consideration should be given to the use of lower doses in this group (Ludwig *et al,* 2009a; Morgan *et al,* 2009; Rajkumar *et al,* 2010). Patient education as well as access to 24-h specialist advice and treatment is crucial in preventing and managing infection in myeloma. Prevention and management of infection in myeloma patients is discussed in more detail in the supportive care guideline (Snowden et al 2011).

Recommendations

- There must be 24-h access to specialist advice for the patient and/or primary care team (Grade A1)
- Any febrile myeloma patient should be treated promptly with broad-spectrum antibiotics. Intravenous antibiotics are required for severe systemic infection or neutropenic sepsis (Grade A1)
- Aminoglycosides should be avoided, if possible (Grade B2)
- There is insufficient evidence to recommend the routine use of prophylactic antibiotics (Grade C2)

5 Myeloma bone disease

5.1 Clinical features of bone disease

Bone disease occurs in 80-90% of myeloma patients. The development of bone disease, either focal or diffuse, can result in pain, pathological fractures/spinal cord compression and hypercalcaemia (Coleman 1997; Croucher and Apperley 1998; Terpos and Dimopoulos 2005) Skeletal events compromise mobility and day-to-day independence, decrease quality of life (Cocks *et al,* 2007; Terpos and Rahemtulla 2004; Vogel *et al,* 2004) and increase overall treatment costs.

5.2 Bone fractures

Long bone fractures require stabilization and subsequent radiotherapy. Radiotherapy is useful to improve pain control and may also promote healing of the fracture site. Where large lytic lesions may cause skeletal instability an orthopaedic opinion should be sought and pre-emptive surgery considered in selected patients. Specialized clinical interventions for pain associated with spinal fractures including vertebroplasty and kyphoplasty are discussed in the supportive care guideline (Snowden et al 2011).

Recommendations

- Local radiotherapy is helpful for pain control; a dose of 8 Gy single fraction is recommended (Grade B1)
- Long bone fractures require stabilization and subsequent radiotherapy; a dose of 8 Gy single fraction is recommended (Grade B1)

5.3 Bisphosphonates

A Cochrane Review of the use of bisphosphonates in myeloma (Djulbegovic *et al,* 2002) included data from 10 placebo-controlled trials of clodronate, pamidronate, or etidronate and from a preliminary report of a trial of ibandronate. Based on a meta-analysis of trial data at that time, the conclusion was that adding bisphosphonates to the treatment of myeloma reduces vertebral fractures and pain but does not improve survival. The evidence also suggested a benefit in both

patients with and without bone disease at presentation. Randomized trials with etidronate, clodronate, pamidronate, zoledronic acid and ibandronate in myeloma patients have now been published (reviewed in (Terpos *et al,* 2009)). Oral etidronate has been shown to be ineffective in myeloma and may cause demineralization (Belch *et al,* 1991). There are as yet no published randomized studies of risedronate or alendronate, while ibandronate failed to show any effect on fracture rates or survival (Menssen *et al,* 2002).

The trials of sodium clodronate (Lahtinen *et al,* 1992; McCloskey *et al,* 2001; McCloskey *et al,* 1998) demonstrated benefit for up to four years in patients starting chemotherapy for the first time, including patients with no lytic lesions. Studies using the nitrogen-containing bisphosphonates have been primarily in patients with more extensive bony disease. Both pamidronate and zoledronic acid have demonstrated their effectiveness in the reduction of skeletal related events (SREs) in this setting (Berenson *et al,* 2001; Rosen *et al,* 2001; Rosen *et al,* 2003). Zoledronic acid and pamidronate appear equally efficacious with regards to SRE prevention although there has been no randomized comparison and no long-term analysis of treatment benefit. Zoledronic acid is however associated with greater improvements in skeletal morbidity and normalization of N-telopeptide of collagen type1 (NTX) in some studies (Rosen *et al,* 2001). The Medical Research Council (MRC) Myeloma IX trial has recently reported with a median follow up of 3.7 years and demonstrated significant benefits of zoledronic acid over sodium clodronate in reduction of SREs (27% vs 35.3% *P=0.0004*, and crucially in overall survival (OS) (50 vs 44.5 months, *P=0.0118*) and progression free survival (PFS) (19.5 vs 17.5 months, *P=0.0179*) respectively (Morgan et al, 2010). There was however a higher incidence of bisphosphonate-associated osteonecrosis of the jaw (BONJ) in the zoledronic acid group (3.5% vs 0.3%). There has also been a suggestion of a survival benefit in the pamidronate trials but this was only demonstrated following subgroup analysis.

Adverse effects on renal function have been reported particularly with the nitrogen-containing bisphosphonates (pamidronate and zoledronic acid) and are most likely if the recommended dose or rate of infusion is exceeded (Barri *et al,* 2004; Berenson *et al,* 1998; Chang *et al,* 2003; Rosen *et al,* 2001). Specific protocols are provided by the manufacturers with regards to administration in patients with renal impairment (see Appendix 2).

Oral calcium and vitamin D supplementation is advised with zoledronic acid. There is no recommendation with pamidronate and it should probably be avoided with sodium clodronate as it may impair absorption of the oral bisphosphonate. All bisphosphonates are associated with a risk of BONJ, but particularly the nitrogen-containing intravenous preparations. This is discussed in detail in the supportive care guidelines (Snowden et al 2011).

Treatment in asymptomatic patients

There is little published evidence to guide the optimal time point to initiate bisphosphonate treatment. A trial of monthly intravenous pamidronate *versus* placebo in newly diagnosed patients not requiring chemotherapy suggested a bone protective effect, although other manifestations of progression were not influenced (Musto *et al,* 2003). Similar results have been suggested with zoledronic acid monthly for one year although one patient did develop BONJ (Musto *et al,* 2008).

Recommendations for bisphosphonate therapy

- Bisphosphonate therapy is recommended for all patients with symptomatic multiple myeloma, whether or not bone lesions are evident (Grade A1)

- Zoledronic acid and pamidronate both show efficacy with respect to SRE prevention (grade A recommendation; level 1b evidence) but early data regarding prolongation of event-free survival (EFS) and OS in a large randomized trial suggest that zoledronic acid should be the bisphosphonate of choice (Grade B1)

- Sodium clodronate is less effective than zoledronic acid but has a significantly lower incidence of BONJ (Grade B1)

- There is no consensus regarding the duration of bisphosphonate therapy. The standard of care to date has been indefinite bisphosphonate therapy. However, given the risk of BONJ, it is reasonable to consider stopping therapy under certain circumstances, such as in those patients who have achieved a CR or VGPR with transplantation and/or a novel therapy combination and have no active bone disease; this should be at the discretion of the treating haematologist. In the absence of definitive data the duration of therapy should take into account individual factors such as remission status, extent of skeletal disease, renal function and patient preference. In patients who do stop bisphosphonate therapy, therapy should be reinstituted at the time of relapse (Grade C2)

- Renal function should be carefully monitored and doses reduced in line with the manufacturers' guidance. For guidance on the use of bisphosphonates in renal impairment, see Appendix 2 (Grade A1)

- At present there is insufficient evidence to make a recommendation for the use of bisphosphonates in patients with asymptomatic myeloma (Grade C2)
- Dental evaluation should be carried out before starting IV bisphosphonate therapy (Grade A1)

6 Renal Impairment

6.1 Incidence and pathophysiology

Renal impairment is a common and potentially serious complication of myeloma occurring at presentation in 20-25% of patients (Knudsen *et al,* 1994) and in up to 50% of patients at some time during their disease (Eleutherakis-Papaiakovou *et al,* 2007; Kyle 1975). It is possible to reverse renal insufficiency in approximately half of patients but the remainder will have some degree of persistent renal impairment and of these, 2-12 % will require renal replacement therapy (Clark *et al,* 1999). Renal failure occurs as a result of damage caused to renal tubules by free light chains (cast nephropathy, or "myeloma kidney"). A variety of other nephrotoxic processes may also contribute to this damage including dehydration, hypercalcaemia, nephrotoxic drugs, and infection (Clark *et al,* 1999; Haubitz and Peest 2006; Penfield 2006). The risk of renal damage is directly proportionate to the level of urinary free light chain excretion and not attributable to the light chain class or the presence or absence of whole M-proteins. Only 2% of patients without urinary free light chain excretion have renal impairment. This percentage increases to 50% with higher levels of urinary free light chain excretion (Drayson *et al,* 2006).
Patients presenting with renal failure have a high early death rate; of 367 newly diagnosed myeloma patients with serum creatinine >199 mmol/l, 29.4% died within 60 days of diagnosis (Augustson *et al,* 2005). In this study 43 of 299 deaths within 60 days were attributed wholly to renal failure. It is therefore critically important to prevent renal failure, or if established, to reverse it as this will significantly improve survival (Knudsen *et al,* 2000).

6.2 Prevention of Renal Failure

Early diagnosis of both new and relapsed myeloma enables early intervention and thus prevention of renal damage (Augustson *et al,* 2005; Drayson *et al,* 2006). A diagnosis of light chain only myeloma and of light chain escape may be missed if urine is not sent to the laboratory and SFLC levels are not measured (Pratt 2008). Relapse with rising levels of free light chain and no change in whole paraprotein (light chain escape) occurs in 5% of IgG and 15% of IgA myeloma patients (Mead and Drayson 2009). Renal function is optimized by maintenance of a high fluid intake, at least 3 litres/day (MRC Working Party on Leukaemia in Adults, 1984) and all patients should be instructed as to the importance of this throughout the course of the disease. Potentially nephrotoxic drugs, including aminoglycosides and non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided.

6.3 Early Management of Renal Failure

The goal of initial treatment is to remove precipitating causes and to rapidly reduce the light chain load delivered to the kidney tubule. Hypercalcaemia must be corrected with bisphosphonates, used with modified doses because the kidney is their only route of excretion (see Appendix 2). Infection must be treated vigorously, nephrotoxic drugs stopped and patients rehydrated. Dehydration from any cause will increase the concentration of light chains delivered to the renal tubule. Renal

recovery can be achieved with intravenous fluid to achieve a urine flow of over 3 litres/ day (MRC Working Party on Leukaemia in Adults,1984). Volume replacement should be guided by monitoring of central venous pressure when renal output is reduced. There is little evidence to support urinary alkalinization (Iggo *et al,* 1997).The advice of a nephrologist should be sought if renal function does not improve within 48 h of initial interventions and there must be clear communication between haematologists and the specialist renal team to optimize outcome. Renal biopsy is desirable to help guide management but is not essential.

Physical removal of light chains by plasma exchange (PE) is theoretically beneficial in cast nephropathy. Data from two early small randomized trials was conflicting (Johnson *et al,* 1990; Zucchelli *et al,* 1988) and the results of a further randomized, controlled trial (Clark *et al,* 2005) were inconclusive. Results of further UK studies of PE and of large pore haemodialysis are awaited. Reducing light chain production from the plasma cell clone is the most effective mechanism of reducing the light chain load to the kidney. High dose dexamethasone alone is effective as a single agent in this setting (Alexanian *et al,* 1992) and can lead to 100-fold falls in SFLC within 2 weeks in sensitive disease. Lower levels are associated with renal recovery (Drayson *et al,* 2009; Hutchison *et al,* 2008).

Oral high dose dexamethasone should be started without delay whilst decisions about definitive chemotherapy are being made. SFLC measurements in the first 2 weeks may identify patients who are not responding to their anti-myeloma therapy. Further work is needed to evaluate how this finding may influence treatment decisions in the future. The high early death rate in patients with myeloma and renal failure is mainly due to infection, which is a major preventable cause of death in these patients. Close observation and early and intensive treatment of infective episodes is essential if this early loss is to be improved.

Recommendations for initial management of renal failure

- Vigorously rehydrate with at least 3 litres of normal saline daily (Grade A1)
- Treat precipitating events eg hypercalcaemia, sepsis and hyperuricaemia and discontinue nephrotoxic drugs, particularly NSAIDs (Grade A1)
- Consider physical methods of removing free light chains from the blood (plasma exchange, large pore haemofiltration) within the context of a clinical trial(Grade C2)
- Administer high dose dexamethasone unless otherwise contraindicated pending initiation of definitive treatment which should be started without delay
- Monitor SFLC levels (Grade B1)
- Identify and treat infection vigorously (Grade A1)

- Patients with renal failure require dose modification of bisphosphonates and the risk of renal adverse events may be greater in patients with impaired renal function. For guidance on use of bisphosphonates in patients with renal impairment, see Appendix 2 (Grade A1)

7 Induction therapy including management of major toxicities and stem cell harvesting

The broad aims of treatment in myeloma are to control disease, maximize quality of life and prolong survival and can be achieved by a combination of specific disease-directed therapy and supportive care. Although high-dose therapy is recommended where possible, many patients will not be able to receive such therapy because of advanced age, co-morbidities or poor performance status. Treatment decisions should be reviewed in an MDT and should take into account individual patient factors and patient choice.

The introduction of novel agents, such as thalidomide, lenalidomide and bortezomib (usually in combination with dexamethasone) has led to a clear improvement in survival of patients with myeloma (Kumar *et al,* 2008a). However, much work is needed to determine the best sequence and combinations of therapies. It is therefore essential that, wherever possible, patients are entered into clinical trials. As many patients are living longer with myeloma, the impact of therapy on quality of life is particularly important.

Many studies both in the transplant and non-transplant settings have suggested a link between the maximal response attained and long-term outcome after initial therapy and that increasing the complete remission rate after transplant results in prolonged progression-free survival (PFS) and OS (Lahuerta *et al,* 2008; van de Velde *et al,* 2007). Improving depth of response is therefore becoming an increasingly important goal.

7.1 Induction therapy prior to high dose therapy (HDT), including management of common side-effects

For patients where HDT is planned, or is a possible future option, the aim of induction treatment is to induce high remission rates rapidly and with minimal toxicity and to preserve haemopoietic stem cell function to ensure successful mobilization of peripheral blood stem cells (PBSC).

Prior to the introduction of novel therapies, the standard of care for patients in whom HDT and autologous stem cell transplantation (ASCT) was planned was the use of induction therapy based on high dose dexamethasone, such as VAD (vincristine, doxorubicin and dexamethasone), or related infusional regimens. These combinations were associated with response rates of 55-84% and CR rates of 8-28% (Alexanian *et al,* 1990; Gore *et al,* 1989; Samson *et al,* 1989) although it should be noted that the current definition of CR is more rigorous. However, there was significant

haematological toxicity and the need for central venous access led to an appreciable incidence of line-related infections and thrombosis.

Table 7 shows a summary of evidence and toxicity profiles for the novel agents. Strategies for preventing and managing known side effects are included in the relevant sections and in Section 7.3.

General prescribing points

- Guidance regarding dose-reduction of cytotoxic agents, such as melphalan and cyclophosphamide, in the setting of low blood counts is well established in local clinical practice guidelines and Summary of Product Characteristics (SPC) documents. As a guide, the neutrophil count is recommended to be >1.0 x 10^9/l and the platelet count >50 to 75 x 10^9/l before commencing treatment. Treatment should be delayed until these levels are achieved, unless cytopenias are considered to be due to marrow infiltration
- Myeloma frequently causes anaemia at diagnosis whereas thrombocytopenia is more common in end-stage disease. The BM reserve generally improves with effective myeloma therapy
- Renal or hepatic impairment may compound drug-induced myelosuppression
- Granulocyte colony-stimulating factor (G-CSF) can reduce/ prevent severe neutropenia and should be considered according to local policies
- Attention should be paid to the SPC
- Prescribing should occur in close consultation with specialist pharmacists

7.1.1 Thalidomide-containing regimens

Thalidomide has a number of mechanisms of action in myeloma including anti-angiogenic activity, inhibition of tumour necrosis factor-α, stimulation of the secretion of α-interferon (IFN-α) and interleukin-2, induction of apoptosis and regulation of adhesion molecule expression (Hideshima *et al,* 2000). It was the first of a number of novel agents responsible for improvements in survival in myeloma and has become widely used as part of induction therapy.

Evidence for use of thalidomide-containing regimens as induction prior to SCT

A retrospective matched case control analysis compared patients treated with VAD as induction therapy with patients treated with thalidomide/dexamethasone. This showed a significantly higher response rate in the thalidomide arm versus the VAD arm ($p<0.001$) (Cavo *et al,* 2005). Since then, several randomized phase III trials have evaluated thalidomide-containing combinations as induction therapy although not all of these trials used these induction regimens specifically as induction prior to high dose therapy. Results of trials comparing thalidomide with conventional induction therapy are summarized in Table 1 of Appendix 3.

In general, the use of thalidomide and dexamethasone as induction does not produce superior response rates post-ASCT. The phase III HOVON (Stichting Hemato-Oncologie voor Volwassenen Nederland) study comparing TAD (thalidomide, doxorubicin and dexamethasone) to VAD showed improved overall response rate, including major response, and improved PFS following ASCT (Lokhorst *et al,* 2010). There was no survival benefit for the thalidomide arm, however, because these patients had a shorter post-relapse survival. The MRC Myeloma IX trial compared CVAD (cyclophosphamide, vincristine, doxorubicin and dexamethasone) with CTD (cyclophosphamide, thalidomide and dexamethasone). Preliminary results have shown higher response rates in the CTD arm but information on the benefit for PFS and OS is awaited. This is the now the most widely used combination in the UK following the demonstration that it can be safely and effectively delivered in a large, multi-centre clinical trial setting. Stem cell mobilization and harvesting are not adversely affected by the use of thalidomide-containing regimens.

Toxicity of thalidomide

The principal non-haematological toxicities of thalidomide and their management are described in Table 8.

7.1.2 Bortezomib-based regimens

Evidence for use of bortezomib-containing regimens as induction prior to SCT

The proteasome inhibitor bortezomib (Velcade, previously PS-341) is active as a single agent in patients with untreated myeloma (Anderson 2006). A phase II study in 60 patients showed a response rate (RR) of 28% with 10% CR but several phase II trials have confirmed higher response rates when bortezomib is combined with dexamethasone and/or chemotherapy in previously untreated patients who are considered eligible for ASCT. These have shown response rates ranging from 66 to 95% with CR rates (where reported) of 6-24% and details of these studies are shown in Table 2 of Appendix 3 .

Two large phase III trials have been reported and provide substantial evidence that bortezomib-based therapy is a successful pre-ASCT induction regimen. The IFM (Intergroupe Francophone du Myélome) group has completed a randomized phase III trial comparing 4 courses of VAD with bortezomib/dexamethasone in 482 patients up to the age of 65 years (Harousseau et al, in press). In this and the HOVON trial, which compared PAD (bortezomib, doxorubicin and dexamethasone) and VAD (Sonneveld *et al,* 2008), the CR or CR/ near CR (nCR) rate increased significantly post-ASCT in the bortezomib-containing arm. In the IFM trial, significant prolongation of PFS was seen but this did not result in longer OS.

Toxicity of bortezomib

Bortezomib requires intravenous administration. The most frequently reported toxicities are shown in Table 9. All are predictable but require active management and specific guidelines have been developed for their prevention and treatment. A proforma for the early detection of side-effects for use in patients on bortezomib therapy has been developed and is shown in Appendix 4. The key to effective use of bortezomib is the optimal management of treatment emergent toxicities allowing the maximum duration of therapy. Recent data from front line protocols incorporating bortezomib suggest that a weekly regimen is as effective and associated with less neuropathy than twice weekly regimens (Gay *et al,* 2009; Mateos *et al,* 2010). In all the trials described above, stem cell mobilization was unaffected by bortezomib therapy and haematological recovery was adequate following stem cell reinfusion after high dose therapy.

Neutropenia secondary to bortezomib is unusual, but thrombocytopenia is a frequent cyclical effect with nadirs around day 11, which usually recover towards baseline by the start of the next cycle. The platelet count should be >30 x 10^9/l to treat and patients may receive platelet transfusions to allow this. If the platelet count is <30 x 10^9/l on day 1, dose reduction should be considered e.g. to 1mg/m^2. Thrombocytopenia tends to become less severe with time on treatment. There are no recommended dose reductions for patients with renal or hepatic impairment. Aciclovir prophylaxis is recommended due to increased incidence of varicella zoster infection. Venous thromboembolic events are not a feature with bortezomib either alone or in combination and hence prophylaxis is not required

7.1.3 Lenalidomide-based regimens

Lenalidomide (Revlimid) is an orally administered thalidomide analogue with a different side-effect profile. It has more potent *in-vitro* activity, including the inhibition of angiogenesis, cytokine modulation and T-cell co-stimulation than thalidomide (Corral and Kaplan 1999; Haslett *et al,* 2003; Hideshima *et al,* 2000).

Evidence for use of lenalidomide-containing regimens as induction prior to SCT

Several phase II studies of lenalidomide with dexamethasone +/- chemotherapy have demonstrated high response rates of between 76 and 91% and are summarized in Appendix 3 (Table 3). In a study of 34 patients treated with a combination of lenalidomide 25 mg daily on days 1-21 of a 28-day cycle and high dose dexamethasone, all patients who underwent stem cell mobilization collected sufficient stem cells. (Rajkumar *et al,* 2005). Despite this, concerns have been raised about failure to harvest adequate stem cells after prolonged lenalidomide treatment and, as a result, it is now recommended that stem cells should be collected within 6 months of initiation of lenalidomide therapy (Kumar *et al,* 2007).

Toxicity of lenalidomide

Lenalidomide is considered to be better tolerated than thalidomide. In particular, it does not cause significant somnolence, neuropathy or constipation. Key lenalidomide toxicities are shown in Table 10. The most frequently seen toxicities occurring grade > 3 are myelosuppression (which can usually be managed with dose reduction and growth factor support if necessary) and thrombosis. Recommendations regarding thromboprophylaxis are described in Section 7.3.2. A full blood count should be performed at baseline, weekly for the first 2 months of treatment and at least monthly thereafter. Dose adjustments are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia. The incidence is higher in patients with impaired renal function (Weber *et al,* 2006). Dose adjustments (Table A of Appendix 2) are recommended within the SPC to manage grade 3 or 4 thrombocytopenia (Table B of Appendix 2) and neutropenia (Table C of Appendix 2) and renal impairment (Table D of Appendix 2).

Neutropenia and thrombocytopenia are the commonest Grade 3/4 toxicities. In relapsed patients the reported incidence was 35.4% and 13%, respectively, in 2 large randomized trials (MM-009 and MM-010) (Dimopoulos *et al,* 2009a). The risk of myelosuppression may be higher in patients who have recently (≤1 year) had high dose therapy and ASCT. Importantly, the incidence of neuropathy is low, grade 3+ neuropathy occurring in less than 5% of patients with relapsed myeloma (Richardson *et al,* 2006).

7.1.4 Combinations involving 2 or more novel agents as induction therapy prior to SCT

There is evidence for high response rates and high CR rates with combinations involving more than one novel agent reviewed in (Lonial and Cavenagh, 2009) but further data are required regarding the toxicity profiles of these combinations and whether these higher response rates translate into longer PFS and OS after ASCT.

Combinations, such as bortezomib, thalidomide, dexamethasone (VTD), have given response rates of 82 to 92% with CR rates of 18-29% (Cavo *et al,* 2009; Rosiñol *et al,* 2009) without an increase in serious adverse events in 3-drug combinations (Cavo *et al,* 2009). Several other combinations have been explored in phase II trials (see Table 4 of Appendix 3).

7.2 Initial treatment when HDT is not planned

The aim of therapy in these usually older and less fit patients is to achieve the maximum durable response with minimal treatment-related toxicity. These patients form a heterogeneous group and have a variable tolerance of therapy. Treatment may need to be modified in patients with poor performance status.

A large meta-analysis showed the combination of oral melphalan and prednisolone (MP) to be as effective as combination regimens including intravenous drugs (Myeloma Triallists' Collaborative Group1998). Melphalan and cyclophosphamide were shown in early randomized studies to be

equally effective (MRC Working Party for Therapeutic Trials in Leukaemia, 1971). Thus, in the past these drugs, usually with prednisolone (P), have formed the mainstay of first line therapy in this patient group.

Thalidomide based regimens–

Use of thalidomide has also been extensively explored in this setting. A phase III study comparing thalidomide and dexamethasone (TD) with dexamethasone in patients with a median age of 65 years showed a significant benefit with regard to response and time to progression (TTP) in the TD group after 4 cycles, albeit with grade 3 or higher non-haematological toxicity being seen in 67% of patients who received TD (Rajkumar *et al,* 2006). Only one study has directly compared TD with MP (Ludwig *et al,* 2009a). This phase III study in 298 elderly patients showed superior responses in the TD arm but similar PFS and TTP in both groups. However, OS was significantly lower in the TD group, and it was thought that this very elderly population (60% of patients between 70 and 79 years) were unable to tolerate the high doses of thalidomide and dexamethasone used.

Five randomized trials have compared oral MP with MPT (melphalan, prednisolone and thalidomide) as first line treatment in elderly patients and the results of these studies are summarized in Table 5 of Appendix 3. Despite variation in the doses of all 3 agents between the 5 studies, all have shown superior response rates and PFS in the MPT arms and two have shown significant prolongation of OS (Facon *et al,* 2007; Hulin 2009). The failure of other studies to produce this benefit was probably due to effective salvage therapy incorporating novel agents at relapse (Gulbrandsen *et al,* 2008; Palumbo *et al,* 2008a; Wijermans *et al,* 2008).

Most randomized studies have shown that thalidomide doses above 200mg/day are poorly tolerated by elderly patients. In general patients receiving MPT in the above trials did experience an increased incidence of side effects, notably cytopenias, thrombosis, fatigue and peripheral neuropathy.
Given the historical equivalence of cyclophosphamide to melphalan, UK investigators have developed an alternative regimen to MPT comprising cyclophosphamide, thalidomide and dexamethasone (CTD). In older less fit patients attenuated doses (CTDa) are given. CTDa was used in the non-intensive arm of the Myeloma IX trial. Early results from this study demonstrate superior response rates for CTDa over MP and suggest similar efficacy to MPT although PFS and OS data are not yet available (Morgan *et al,* 2009).

Bortezomib- and lenalidomide-based regimens

The newer agents, bortezomib (Velcade, V) and lenalidomide (Revlimid, R) are also effective when used in combination with steroid +/- alkylator. A phase III study comparing M, P and bortezomib (VMP) with MP showed superior response rates , PFS and OS in the VMP group (San Miguel *et al,* 2008b). This included a 30% CR rate vs 4% with MP, $p<0.001$) and median PFS 24 month vs 16.6 months with MP. The VMP regimen was generally well tolerated, although peripheral neuropathy

(grade 3 or above) affected 13% of patients. This resolved or improved in 75% of cases in a median of approximately 60 days. Patients receiving VMP also had a higher incidence of gastro-intestinal complications and fatigue. More recent trials have investigated once weekly bortezomib in a modified VMP which results in similar response rates but reduced toxicity, especially neurotoxicity (Mateos *et al,* 2010). A combination of M, P and lenalidomide (MPR) is also being explored. A phase I/II study produced comparable response rates to MPT with a low incidence of non-haematological adverse events (Palumbo *et al,* 2007). The relative efficacy of lenalidomide with low dose dexamethasone (Rd) when compared with melphalan-based regimens is now being tested in a phase III trial (Palumbo et al, 2009).

A randomized trial of 445 patients comparing lenalidomide with either high dose or low dose dexamethasone in newly diagnosed myeloma showed significant benefits for low dose dexamethasone in terms of OS at 1 year (96% vs 86% p=0.0002) (Rajkumar *et al,* 2010). For this reason, the trial was stopped early and patients on high-dose dexamethasone therapy were crossed over to low-dose therapy. The decision regarding dexamethasone dose should be made on an individual patient basis based upon assessment of co-morbidities, tolerance and performance status.

Plasma cell leukaemia

The outcome with conventional chemotherapy is poor, as the reported median survival is 8-12 months (Dimopoulos *et al,* 1994; Garcia-Sanz *et al,* 1999) although an improvement in outcome has been reported with autologous transplantation (Drake *et al,* 2010) and bortezomib treatment (Finnegan *et al,* 2006).

Summary of treatment recommendations

General

- Chemotherapy prescription should be undertaken by an experienced clinician with input from a specialist chemotherapy-trained pharmacist (Grade A1)
- SPC recommendations for dose adjustments of chemotherapy drugs and use of G-CSF support should be followed wherever possible (Grade A1)
- Patients should be appropriately dosed, to allow for renal and liver function (Grade A1)
- Patients with cytopenias at baseline due to limited marrow reserve require more frequent monitoring and dose adjustment (Grade A1)
- All patients should be considered for entry into a clinical trial (Grade A1)
- The choice of therapy should take into account patient preference, co-morbidities and toxicity profile (Grade A1)

Specific treatment recommendations for Induction therapy prior to high dose therapy (HDT)

- VAD or single agent dexamethasone should no longer be routinely used as induction therapy (Grade A1)
- Induction regimens should contain at least one novel agent (Grade A1)
- Examples of induction regimens that are superior to VAD in terms of response rates include CTD, TAD, bortezomib/dexamethasone and PAD. (Grade A1)
- Decisions regarding the most appropriate induction for individual patients will require the assessment of a number of factors, such as renal function, thrombotic risk and pre-existing neuropathy although it is appreciated that some agents are not routinely funded as initial therapy in the UK. CTD is the combination of which there is the most clinical experience in the UK (Grade C2)

Specific treatment recommendations for older and/or less fit patients in whom HDT is not planned initial therapy

- Induction therapy should consist of either
    - a thalidomide-containing regimen in combination with an alkylating agent and steroid such as MPT or CTDa (Grade C2) or
    - bortezomib in combination with melphalan and prednisolone (Grade C1).

Specific treatment recommendations for patients with plasma cell leukaemia and rarer myeloma subtypes

Recommendations (all are Grade C based on level IV evidence)

- The use of initial treatment with bortezomib and autologous stem cell transplantation should be considered in responding patients with plasma cell leukaemia (Grade C1)
- IgD, IgE and IgM myeloma are associated with a poor outcome but there is insufficient data to support specific alternative treatment strategies at this time. (Grade C1)

7.3 Prevention and management of treatment related complications of therapy

7.3.1 Peripheral neuropathy

The investigation and management of peripheral neuropathy is described in detail in the supportive care guideline (Snowden et al 2011). Some of the key recommendations are listed below:

- Peripheral neuropathy is common at diagnosis and as a result of many myeloma therapies
- Peripheral neuropathy and autonomic neuropathy symptoms and signs should be actively sought and sequentially graded during the course of therapy using a scale, such as the National Cancer Institute Common Toxicity Criteria (http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcv20_4-30-992.pdf) to provide an objective assessment and allow identification of trends (Grade A1)

- Any patient who develops a significant (eg. >NCI grade 2) or progressive peripheral or autonomic neuropathy following treatment should be managed with graded dose reduction or drug withdrawal. Guidelines for dose reductions of thalidomide and bortezomib are shown in Table 11. Continuation of dose intense treatment in the face of neuropathy may cause permanent neurological damage. (Grade A1)
- The management of peripheral neuropathy should include symptom control along with treatment of any potentially reversible causes. Optimal management of co-morbid causes such as diabetes mellitus may also improve tolerance of neurotoxic drugs (Grade A1)
- Neuropathic pain is poorly responsive to simple analgesics, NSAIDs and opioid drugs. Neuromodulatory agents are being increasingly recommended to treat neuropathic pain. Patients with progressive neuropathic pain despite appropriate analgesia should be referred promptly for specialist advice regarding pain management (Grade A1)

7.3.2 Thromboprophylaxis

Myeloma and other plasma cell disorders have a well-established association with venous thromboembolism (VTE) (Srkalovic *et al,* 2004). Active disease, cancer therapies, infection, previous VTE, immobility and paraplegia are all well-recognized additional risk factors for VTE in hospitalized patients. Thalidomide and lenalidomide have been demonstrated to further increase this risk. Use of thromboprophylaxis and treatment of both thrombosis and bleeding problems in myeloma patients are discussed in detail in the Guidelines for Supportive Care in multiple myeloma (Snowden *et al* 2011)(. Key recommendations from that document are listed below.

Recommendations

- Cancer, cancer therapies, infection, previous VTE, immobility, obesity, paraplegia, erythropoietin treatment, dehydration and renal failure are all well-recognized risk factors VTE, particularly in hospitalized patients. As with other areas of thromboprophylaxis, a risk stratified approach is appropriate in patients with myeloma. (Grade A1)
- A risk assessment model for the prevention of venous thromboembolism in multiple myeloma patients treated with thalidomide or lenalidomide is contained within the Guidelines for Supportive Care in multiple myeloma (Snowden *et al* 2011)(adapted from (Palumbo *et al,* 2008b)
- All patients who are due to start thalidomide or lenalidomide-containing therapy should undergo a risk assessment for VTE and prospectively receive appropriate thromboprophylactic measures. (Grade A1)
- In patients receiving thalidomide or lenalidomide, aspirin 75325 mg may be considered as VTE prophylaxis in low risk patients only (i.e. without risk factor present), unless contraindicated (Grade B2)

- Patients receiving thalidomide or lenalidomide in addition to combination chemotherapy/anthracyclines/high dose steroids, or those with two or more myeloma/individual risk factors should be offered prophylaxis with LMWH (high risk prophylactic dose) or dose-adjusted therapeutic warfarin, unless contra- indicated. There is no role for fixed, low dose warfarin (Grade B1)
- The duration of thromboprophylaxis remains unclear but should be guided by risk factors such as active disease (e.g. for the first 4–6 months of treatment until disease control achieved) and de-escalated or discontinued unless there are ongoing significant risk factors (Grade C2)
- Treatment of confirmed VTE should follow current practice guidelines using adjusted dose warfarin or LMWH and appropriate monitoring (Grade A1)

7.4 Can novel agents overcome the poor prognosis associated with adverse cytogenetic abnormalities?

This group comprises some 15-20% of newly diagnosed patients, and includes those with the following cytogenetic abnormalities: t(4;14), t(14;16), t(14;20), del(17q) or non-hyperdiploid disease (Stewart *et al,* 2007). Although del(13q) by metaphase cytogenetic analysis is an adverse prognostic marker, these patients invariably have a t(4;14) translocation. Gain of chromosome (1q21) has also recently been described as conferring a poor outcome, however, this occurs in association with t(4;14) and del(13q), and may not be an independent prognostic marker (Fonseca *et al,* 2006).

An important unanswered question is whether the use of novel agents may overcome cytogenetically-defined poor prognosis disease. In the VISTA (Velcade® as Initial Standard Therapy in Multiple Myeloma) study (Mateos *et al,* 2008) in the non-transplant setting, patients with high risk disease who received bortezomib had equivalent response rates, PFS and OS to standard risk patients but the number of patients in this group was small. In the IFM study, pre-ASCT induction with bortezomib partially overcame the poor prognosis of t(4;14) disease (67 patients), but had no impact on 17p disease (51 patients) (Avet-Loiseau *et al,* 2009). In 16 patients with high risk disease treated with lenalidomide and dexamethasone, response rates and survival were similar to standard risk patients, albeit with shorter duration of response (Kapoor *et al,* 2009). All these data are derived from retrospective sub-analyses of trials, and prospective data on larger patient numbers with longer follow up are needed to establish the role of novel agents in the setting of high risk disease. Available information to date, however, suggest that bortezomib may be able to overcome the poor prognostic impact of some genetic subtypes, such as t(4;14) disease.

Conclusions

- Novel agents have increased the overall and complete remission rates if used pre-ASCT (Grade A1)

- Confirmation is needed that these higher response rates translate into longer PFS and OS after ASCT (Grade C2)
- Further data regarding a number of combinations are required, particularly those containing more than one novel agent (Grade C2)

7.5 Stem cell harvesting after induction therapy including novel agents

Duration of induction treatment prior to SCT

The majority of patients achieve maximum response to induction therapy after 4 to 6 cycles. Response should be assessed after each cycle. Although CR prior to HDT is a good prognostic factor, there is currently no evidence that prolongation of induction treatment to achieve a CR improves outcome. It is currently therefore recommended to treat to at least PR, which usually occurs within 4 to 6 cycles and to switch to an alternative regimen if there is evidence of progressive disease after 2 cycles or less than PR after 4. The treatment of refractory disease is discussed in more detail in Section 8. Alternatively, in responses <PR it is also reasonable to proceed directly to HDT after completion of 4 cycles of induction therapy if stem cells can be successfully harvested.

Stem cell mobilization

Mobilization with cyclophosphamide and G-CSF may overcome the effects of lenalidomide (Mark *et al,* 2008) and is recommended if induction therapy with a lenalidomide-containing regimen has continued for > 4 cycles.

Recommendations (all are Grade C recommendations; level IV evidence)

- Peripheral blood stem cell harvesting (PBSCH) should be carried out within 4-6 cycles for all induction regimens that incorporate a novel agent (Grade B1)
- If induction therapy with a lenalidomide-containing regimen has continued for > 4 cycles, mobilization with cyclophosphamide and G-CSF is recommended (Grade C2)
- Ideally patients should undergo stem cell mobilization within 6 to 8 weeks of completion of induction therapy (Grade B1)

7.6 Chemotherapy in Patients with Renal Failure

In addition to the steps described in Section 6, effective treatment of myeloma is the most successful way of ensuring renal recovery. Regimens that can be used without dose reduction in renal impairment and that produce the highest response rate and most rapid responses should theoretically produce the highest rates of renal recovery. It is essential to understand how agents should be used in the presence of renal impairment to ensure maximal safety and efficacy (see Table 12).

Melphalan

Melphalan is hydrolysed and excreted via the kidneys and there is concern that BM suppression may develop if full doses are used in patients with renal impairment. The manufacturer recommends that initial doses of melphalan should be reduced by 50% if the glomerular filtration rate (GFR) is < 40-50 ml/min, and that it should not be used in patients in whom the GFR is below 30 ml/min. However this is at variance with data which shows that the extent of drug accumulation is variable in each individual and cannot be predicted from the degree of renal impairment (Osterborg *et al,* 1989) and also that, even with doses of melphalan 25 mg/m^2 intravenously, patients with severe renal impairment, including dialysis dependency, did not have longer periods of leucopenia nor adverse OS (Vigneau *et al,* 2002). A retrospective analysis of data from patients with renal impairment treated in clinical trials led Carlson et al (2005) to propose a 25% initial dose reduction with titration according to BM toxicity for subsequent courses.

Cyclophosphamide metabolites are excreted in the urine. Manufacturers recommend a dose reduction of 25% if the GFR is 10-50 ml/min, and of 50% if GFR is less than 10 ml/min. Clinical experience suggests it is safe to titrate the dose in subsequent courses according to response.

Anthracyclines and high dose dexamethasone

Doxorubicin and dexamethasone are commonly used agents, particularly in combination with novel agents (e.g. PAD) and do not require dosage adjustment in the presence of renal impairment even if it is severe (Aitchison *et al,* 1990).

Thalidomide

The pharmacokinetics of thalidomide seems to be unaltered in patients with renal dysfunction (Eriksson *et al,* 2003). Less than 1% of thalidomide is excreted unchanged in the urine and it is not hepatically or renally metabolized to any large extent, appearing to undergo non-enzymatic hydrolysis in plasma to form multiple degradation products. Manufacturers do not recommend dosage reduction. Although the clearance of thalidomide is increased during dialysis it appears unnecessary to give a supplementary dose. A report of thalidomide use in 20 patients with renal impairment did not show any increase in toxicity (Tosi *et al,* 2004) although there have been case reports of hyperkalaemia and tumour lysis syndrome. Less than 3% of thalidomide is excreted unchanged in the urine, however metabolically active hydrolytic products formed via non-enzymatic processes are also present in plasma and urine and their major route of excretion was is the urine (>90%). The manufacturers recommend that patients with severe renal impairment should be carefully monitored for adverse reactions.

Bortezomib

In vitro studies indicate that bortezomib is metabolized primarily through oxidative deboronation by the liver cytochrome P450 system and that early disposition kinetics of bortezomib are not affected by creatinine clearance (range <30 ml/min to >80 ml/min) in patients (Bortezomib SPC). Bortezomib can therefore be used in renal impairment without dose reduction. There have been no large prospective randomized studies of the use of bortezomib in patients with myeloma and renal impairment. However, a number of studies have shown that bortezomib either alone, or in combination with other agents, produces similar response rates in these patients to those seen in patients with normal renal function and that there is no excess toxicity. These include sub-analyses of patients with renal impairment in a number of large studies (Dimopoulos *et al,* 2009b; Jagannath *et al,* 2005a; San Miguel *et al,* 2008c). Median time to first response in the VISTA trial was 1.4 months with VMP compared to 3.5 months with MP (Dimopoulos *et al,* 2009b). Whilst there are a number of studies showing high levels of renal recovery using bortezomib containing regimens (Chanan-Khan *et al,* 2007; Kastritis *et al,* 2007; Roussou *et al,* 2008; Ludwig et al, 2009b) there is no randomized clinical trial evidence to justify recommendation of its routine use in this setting.

Lenalidomide

There are limited data on the clinical use of lenalidomide in renal failure but a pharmacokinetic study in patients with varying degrees of renal impairment following a single dose of lenalidomide 25 mg orally showed that lenalidomide is substantially excreted by the kidneys (Chen *et al,* 2007) with a mean urinary recovery of unchanged lenalidomide of 84% of the dose in subjects with normal renal function. Recovery declined to 43% in subjects with severe renal impairment (creatinine clearance < 30 ml/min), and still further in end stage renal impairment. This study also showed that a 4-h haemodialysis removed 31% of lenalidomide. Lenalidomide should be used with caution and appropriate dose reductions in patients with renal impairment because of the increased risk of cytopenias. Recommended dose reductions for patients with renal impairment are shown in Table D of Appendix 2.

Recommendations

- **Dexamethasone** alone can be given as initial treatment pending decisions on subsequent chemotherapy and the outcome of full supportive measures (Grade B1)
- **Melphalan** can be considered for patients with renal impairment in whom other regimens may be relatively contraindicated. The dose should be reduced by 25% in the first course if GFR < 30 ml/min and titrated against marrow toxicity in subsequent courses (Grade C2)
- **Cyclophosphamide** can be used with a dose reduction of 25% if the GFR is 10-50 ml/min, and of 50% if GFR is less than 10 ml/min and titrated in subsequent courses according to response (Grade A1)

- **Thalidomide** can be used without dose modification in patients with renal failure (Grade A1)
- **Bortezomib** can be safely used in myeloma patients with renal failure including those on dialysis at the standard starting dose of 1.3 mg/m^2. However, because of limited data on toxicity, patients with renal impairment (creatinine clearance ≤ 30 ml/min) and patients on haemodialysis should be closely monitored for toxicity. Although there is mounting evidence that bortezomib appears effective in this setting, further studies are needed to confirm results derived from subgroup analyses of large randomized trials and data from other non randomized studies (Grade A1)
- **Lenalidomide** can be given in patients with renal impairment but dose adjustments as recommended by the manufacturer should be implemented (Grade A1)

8. Myeloma refractory to induction therapy

Primary Refractory myeloma is defined as disease that is non-responsive in patients who have never achieved a *minimal response or better with any therapy*. It includes patients who never achieve MR or better in whom there is no significant change in M protein and no evidence of clinical progression and also patients with progressive disease(Rajkumar *et al,* 2011). The principles of managing primary refractory disease differ depending on whether the patient is still considered a candidate for high dose therapy.

Patients for whom high dose therapy remains an option

It is important to distinguish patients who have refractory but non-progressive disease, i.e. are clinically stable, from those who have evidence of disease progression on induction therapy. There is evidence that the former group still stand to benefit from consolidation with high dose therapy (Alexanian *et al,* 1994a; Alexanian *et al,* 1994b; Kumar *et al,* 2004). The decision of whether to proceed straight to PBSCH and HDT may depend on co-morbidities, toxicity from previous treatment, and, perhaps, degree of BM infiltration. Such decisions should ideally be undertaken in an MDT meeting.

In cases where the BM is heavily infiltrated, 2 options are available

1. Use a non-cross-reactive mobilization regimen such as ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) (D'Sa *et al,* 2004) in patients with normal renal function to achieve further cytoreduction prior to HDT
2. For patients who are fit enough (sufficient BM reserve, no prohibitive toxicity), use of a salvage regimen prior to stem cell harvesting and HDT is recommended to achieve a greater depth of response as this correlates with improved outcome (Morris *et al,* 2004).

Patients with progressive disease on first-line therapy should receive salvage treatment. These patients have a bleak outlook, and often have poor genetic markers. It is important that such patients are identified early so that salvage therapy can be instituted before further organ damage occurs. Careful monitoring of urinary Bence-Jones protein (BJP) is important to avoid renal damage, and salvage regimens that include platinum agents should be avoided in patients with significant BJ proteinuria (>1 g/24 h).

Where possible, patients should be entered into clinical trials. Outside trials, a bortezomib-based regimen should be used, if the patient received thalidomide as part of their induction therapy. If they did not, a thalidomide-containing regimen is an option eg. CTD or DT-PACE (dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide) (Lee et al, 2003a). Other alternative regimens include platinum-based regimens (see above), which can also be used as mobilising chemotherapy together with growth factors, or lenalidomide–containing regimens for patients with ≥grade 2 peripheral neuropathy.

Patients for whom SCT is (no longer) an option

Disease that is non-responsive to initial treatment may remain clinically stable with no evidence of either clinical or laboratory progression for prolonged periods and therefore these patients may not require immediate further treatment but should be closely monitored (MRC, unpublished data). Second-line treatment for those requiring therapy should be a combination including an alternative novel agent eg. VMP in patients who have received upfront CTDa.

Recommendations

- All patients should be considered for entry into a clinical trial (Grade A1)
- For patients intolerant of thalidomide, or refractory to first-line therapy, a bortezomib-based salvage regimen is recommended. (Grade B2)
- Patients with ≥grade 2 peripheral neuropathy should receive a lenalidomide-based regimen (Grade B1)

9. High dose therapy and autologous stem cell transplantation (ASCT)

There is more than 20 years experience of HDT and ASCT in the management of myeloma since the efficacy of high dose melphalan in the treatment of high-risk myeloma and plasma cell leukaemia was first reported (McElwain and Powles 1983). ASCT has become the first line standard of care in those deemed biologically fit enough for this option mainly because of the low transplant-related mortality (TRM) and prolongation of EFS resulting in improved quality of life. Four pivotal randomized studies have been published comparing combination chemotherapy with a high dose approach as first-line therapy for newly diagnosed myeloma patients aged up to 65 years. In most of these studies, maintenance IFN was given in both arms. The results of these studies are summarized in Table 6 of Appendix 3.

Stem cells are now almost exclusively derived from peripheral blood following stimulation with growth factors with or without chemotherapy. The optimal regimen for mobilizing PBSC is unclear but cyclophosphamide (1.5 - 4 g/m^2) with G-CSF is widely used. Purging harvested stem cells with monoclonal antibodies and/or CD34$^+$ stem cell selection does reduce contamination with tumour cells but does not influence the relapse risk (De Rosa *et al,* 2004; Stewart *et al,* 2001).

9.1 Conditioning

High dose melphalan (200 mg/m^2) remains the standard conditioning prior to ASCT. Recent studies have shown that the dose of melphalan can be increased to 220 mg/m^2 (Garban *et al,* 2006), with improved PFS compared with historical controls, or to 240–300 mg/m^2, in combination with amifostine, (Reece et al 2006) but at the cost of increased toxicity. The addition of total body irradiation (TBI) results in increased toxicity (Moreau *et al,* 2002) with no improvement in response rate or PFS, whilst combination chemotherapy increases the toxicity (Benson *et al,* 2007; Capria *et al,* 2006; Vela-Ojeda *et al,* 2007). Bortezomib has shown synergistic effects with melphalan without prolonged haematological toxicity. The recently reported IFM phase II study enrolled 54 untreated patients to receive bortezomib (1 mg/m^2 x 4) and melphalan (200 mg/m^2) as conditioning regimen (Roussel *et al,* 2010). The authors reported a response ≥VGPR in 70% of patients and 32% CR. No toxic deaths were observed with minimal peripheral neuropathy. Due to limited follow-up, response durability data are not yet available (Roussel *et al,* 2010).

9.2 Age

Though to date randomized controlled data (RCT) data on use of ASCT have related mostly to patients ≤65 years, results have indicated that, in selected patients aged >65 years, outcomes are similar to those in younger patients (Jantunen 2006; Reece *et al,* 2003; Siegel *et al,* 1999). Data from the ABMTR (Reece *et al,* 2003) comparing the outcome of 110 patients aged >60 years with 382 patients aged <60 years showed no difference in TRM, EFS or OS. Over 70 years, the toxicity of melphalan 200 mg/m^2 is increased, with a TRM of 16% reported in one series (Badros *et al,* 2001a). An alternative HDT is modified/intermediate dose melphalan, as reported by (Palumbo *et al,* 2004), where 2 cycles of intermediate dose melphalan (100 mg/m^2; IDM) with PBSC support was compared with 6 cycles of MP in patients aged 65-70 years in a RCT, demonstrating a median OS of 58 months with IDM compared to 37.2 months for MP. Kumar et al (2008b) compared a group of 33 patients ≥70 years at the time of HDT with a group of 60 patients <65 years. Despite the fact that more of the elderly patients received a reduced dose of melphalan, the overall response rate and TTP was similar between the two groups. These results indicate that ASCT can be safely performed in patients aged >65 years if care is taken with patient selection, taking into account pre-existing co-morbidities and performance status. Limited data exist to demonstrate that stem cell yields in mobilized blood of patients >60 years are lower and that this can affect platelet recovery (Fietz *et al,* 2004; Morris *et al,* 2003).

9.3 Timing of ASCT

The encouraging results reported with novel agents have challenged the role of ASCT as part of upfront therapy. Several groups have reported early results of prospective studies evaluating the use of ASCT at the time of disease progression after initial induction and consolidation using novel agent combinations. It is, however, likely that ASCT will further increase the rate and depth of responses achieved with induction therapy with a consequent improvement in PFS. There is therefore currently no evidence to support deferral of the first ASCT until the time of first relapse, though prospective studies are underway to explore this possibility further.

9.4 Single versus tandem autologous stem cell transplant

Barlogie et al (1997) pioneered the use of tandem ASCT in the early management of myeloma in the Total Therapy I program, producing a CR rate of 41% and median OS of 79 months. The IFM94 trial was the first randomized study comparing single and tandem transplants, reporting improved EFS (30 vs 25 months) and OS (58 vs 48 months) (Attal *et al,* 2003). However, the recently published systematic review of 6 RCTs including more than 1800 patients failed to demonstrate an improvement in OS or PFS with the use of tandem ASCT in previously untreated patients (Kumar *et al,* 2009a). Two studies suggest that the second procedure is most beneficial in those individuals that have not achieved at least a VGPR (>90% reduction in serum monoclonal protein) with the first transplant (Attal *et al,* 2003; Cavo *et al,* 2007).

An alternative strategy is to collect sufficient stem cells to support two ASCT but to defer the second ASCT until the time of relapse and this approach is increasingly employed. Individuals with the best outcome following a 'deferred' second ASCT are those achieving a first progression-free interval of at least 2 years following their first transplant (Mikhael *et al,* 2004). Definitive recommendations regarding the use of a second ASCT at the time of relapse cannot be made, especially in light of emerging new biological agents. It is recommended that the use of ASCT in the relapse disease setting should, where possible, be performed as part of a clinical study protocol, such as the current joint UKMF/ British Society of Bone Marrow Transplantation (BSBMT) study, Myeloma X.

9.5 High Dose Therapy in Renal Failure

High dose therapy with ASCT has been reported by several centres as a feasible treatment modality in patients with renal failure including those patients requiring dialysis. The use of melphalan at 200 mg/m^2 is associated with a high TRM (16 to 29%) in patients on dialysis (Knudsen *et al,* 2005; San Miguel *et al,* 2000). This compares with a TRM of only 5% in a series of 38 patients with renal failure not on dialysis receiving melphalan 200 mg/m^2 reported by Sirohi *et al,* (2001) and 1 out of 17 patients died who received melphalan at 100mg/m^2 whilst on dialysis (Raab *et al,* 2006). A retrospective BSBMT study looking at high-dose melphalan in 31 patients (27 with myeloma), of whom 23 were on dialysis, conditioned with doses of melphalan 60 – 200 mg/m^2 recorded a TRM of

19% (Bird *et al,* 2006). All studies describe up to 24% of patients coming off dialysis post-transplant (Bird *et al,* 2006; Lee *et al,* 2004).

The largest series of reported patients is from the Little Rock team. In an initial report (Badros *et al,* 2001b), severe toxicities, were observed in 60 patients receiving melphalan 200 mg/m^2, leading them to reduce the dose in subsequent patients to 140 mg/m^2. The threshold for melphalan dose reduction was a creatinine of over 179 mmol/l, equivalent to a GFR of <30 ml/min.These data were extended in a subsequent report, showing a TRM of 19% in 59 patients on dialysis at the time of transplant, 27 of whom had received melphalan 200 mg/m^2 (Lee *et al,* 2004). Even at reduced doses of melphalan, toxicity can be significant with prolonged mucositis and hospitalization (Raab *et al,* 2006). The response rates in patients are similar to matched controls.

Recommendations

- HDT with ASCT should be part of primary treatment in newly diagnosed patients up to the age of 65 years with adequate performance status and organ function (Grade C1)
- HDT with ASCT should be considered in patients aged >65 years with good performance status (Grade C1)
- Conditioning with melphalan alone, without TBI, is recommended (Grade B1). The usual dose is 200 mg/m^2 but this should be reduced in older patients (over 65-70 years) and those with renal failure (see below)
- Planned double ("tandem") ASCT cannot be recommended on the current evidence. However, it is recommended that enough stem cells are collected to support two high dose procedures in patients with good performance status (Grade B1)
- Purging is not of clinical benefit and is not therefore recommended (Grade C1)
- HDT and ASCT may be considered for patients with severe renal impairment (creatinine clearance/GFR <30 ml/min) but the dose of melphalan should be reduced to a maximum of 140 mg/m^2 (Grade B2) and the procedure should only be carried out in a centre with special expertise and specialist nephrology support (Grade C1)

10. Allogeneic Stem Cell Transplantation (AlloSCT)

10.1 Myeloablative (full intensity, FI) allogeneic matched family donor (MFD) stem cell transplantation

AlloSCT can result in long-term disease-free survival but its role in the management of patients with myeloma has been controversial because of the high TRM and morbidity, primarily related to co-morbidities and advanced age (Gahrton *et al,* 1991). However, outcomes have improved significantly over time. In cohorts transplanted from 1983-1993 and 1994-1998, TRM decreased from 46% to 30% (Gahrton *et al,* 2001). Three key studies in the area of FI AlloSCT have reported results: the US intergroup (Barlogie et al 2006a), the Hovon group (Lokhorst et al, 2003) and BSBMT (Hunter et al, 2005). These results are summarized in Table 8. The reported TRM of 34-54% demonstrated the limitations of this type of conditioning despite the long-term EFS of 22-36% and OS 28-44% with

follow-up between 5-7 years. Although these studies examined variations in the conditioning used, including T-cell depletion, no significant impact on TRM was noted with the exception of the superiority of melphalan over cyclophosphamide (Hunter et al, 2005).

Patient selection through careful pre-transplant assessment is important. Co-morbidity scores may be of value, and may be of greater significance than biological age. Outcome after FI AlloSCT is inferior in patients transplanted beyond first remission or in patients with refractory disease (Crawley *et al,* 2005; Maloney *et al,* 2003). The remission status post-transplant is also important, with the achievement of a molecular CR being associated with a very low risk of relapse (Corradini *et al,* 2003). Prior ASCT is associated with poorer outcomes with myeloablative conditioning (Crawley *et al,* 2007; Hunter *et al,* 2005). A negative impact on outcome is also seen with a prolonged time to transplant and with donor/recipient sex-mismatching.

The purest 'proof of principle' of the activity of a graft-versus-myeloma (GvM) effect is the efficacy of donor lymphocyte infusions (DLI) at the time of relapse of disease. The largest series reported (Lokhorst *et al,* 2004), demonstrated that there is clearly a DLI-mediated GvM. Importantly, tumour response was strongly associated with the presence of graft-versus-host disease (GvHD). These data indicate that GvM and GvHD are closely related and largely overlapping phenomena. There are emerging data that concurrent treatment with DLI and novel therapies can increase response rates (Kröger *et al,* 2004). DLI should be considered for patients with relapsed/persistent disease.

10.2 Reduced intensity conditioned (RIC) AlloSCT

To reduce TRM and to permit the application of AlloSCT to older, less fit patients, reduced intensity conditioned AlloSCT (RIC AlloSCT) has been explored. Several studies have shown that this approach is feasible with a significant reduction in TRM. As the conditioning is less cytoreductive, RIC transplants are dependent to a large extent on GvM. One strategy is to perform sequential ASCT/RIC AlloSCT such that minimal disease burden is present at the time of AlloSCT, allowing time for the GvM to be effective. The results of a number of these studies are summarized in Table 8 of Appendix 3. The Seattle group has studied this approach using sequential ASCT followed by a T-replete, low-dose TBI-based RIC AlloSCT (Maloney *et al,* 2003). A day 100 TRM of 0% and 48 month OS and PFS values of 69% and 45% respectively have been reported, with a low incidence of acute but a high incidence of chronic GvHD.

A number of Phase II studies have reported similar findings (Le Blanc *et al,* 2001; Gerull *et al,* 2005; Mohty *et al,* 2004; Perez-Simon *et al,* 2003; Rotta *et al,* 2009). In these studies, the presence of chronic GvHD was associated with the achievement of CR and OS/PFS. In a retrospective EBMT study, Crawley et al (2005) showed that the best outcomes were associated with the development of limited chronic GvHD, with T cell depletion being associated with significantly higher relapse rates. Taken together, these data suggest that clinically effective GvM is intimately associated with GvHD and that, by implication, strategies designed to abrogate GvHD could have deleterious effects

on disease control. Severe GvHD is tolerated poorly by older patients and impacts significantly on quality of life and is an important cause of late mortality after AlloSCT.

Several "biological" (donor versus no donor) studies have been reported (Garban et al, 2006; Bruno et al, 2007; Rosinol et al, 2008), summarized in Table 7 of Appendix 3. TRM rates of <20% are reported with 29 - 80% EFS and 41 - 80% OS resulting from short and variable reported follow-up. In these studies, differences in patient selection/ characteristics (eg. del 13q, high B_2-microglobulin patients versus unselected) conditioning and GvHD incidence are likely to have resulted in the observed differences in outcomes. In at least one of the studies, there were no event-free survivors at 5 years (Garban *et al,* 2006). Recently, longer term results (median follow up 6.3 years) of 102 patients from the Italian group have been published (Rotta *et al,* 2009). Forty-two percent of patients developed grade 2 - 4 acute GvHD and 74% extensive chronic GvHD. Five-year OS and PFS were 64% and 36%, respectively but the median time to relapse was 5 years. Theses data indicate a continuing problem with relapse, including late events and extramedullary relapse and the high rate of chronic GvHD is likely to result in further TRM. No prospective trials have compared ablative with RIC AlloSCT in this setting. However, an EBMT analysis (Crawley *et al,* 2007) has shown similar OS with both approaches. RIC AlloSCT patients had a lower TRM but a higher relapse rate and lower PFS.

10.3 Matched unrelated donor (MUD) AlloSCT

In many diseases, outcomes with MUD AlloSCT have improved with time and, in many settings, have become equivalent to matched sibling transplantation. However, retrospective studies in myeloma have shown a significantly higher TRM than with sibling AlloSCT (Shaw *et al,* 2003) and as a result, myeloablative MUD AlloSCT is not currently recommended and should only be carried out in the context of prospective clinical trials.
The role of RIC MUD AlloSCT remains to be defined although encouraging results have been reported, with short-term TRM of approximately 20% (Kröger *et al,* 2002; Shaw *et al,* 2003). Further prospective trials are warranted in order to better define the role of RIC MUD AlloSCT for patients with myeloma.

Recommendations

- Treatment decisions that involve AlloSCT are some of the most difficult for patients. Patients need to be fully informed and involved in the decision making process. Young patients with matched sibling donors who are interested in pursuing curative therapy should be referred to a haematologist with an interest in allografting myeloma patients so that they gain an understanding of the risks and benefits of this procedure (Grade C2)
- Allogeneic SCT should be carried out in EBMT accredited centres where data are collected prospectively as part of international transplant registries and, where possible, should be carried out in the context of a clinical trial (Grade A1)
- Allogeneic transplant procedures for patients with myeloma in first response should only be considered for selected groups because of the risk of significant transplant-related morbidity and mortality (Grade C2).

- A myeloablative MFD AlloSCT should only be considered in selected patients up to the age of 40 years who have achieved at least a partial response to initial therapy (Grade C2).
- A myeloablative MUD AlloSCT is not recommended except in the context of a clinical trial (Grade C2).
- A RIC MFD or MUD AlloSCT is a clinical option for selected patients preferably in the context of a clinical trial. If carried out, RIC AlloSCT should generally be performed following an autograft, early in the disease course in patients with responsive disease (Grade C2)
- DLI should be considered for patients with persistent or progressive disease following transplantation or for mixed chimerism. If given for disease progression, cytoreduction should probably be carried out first (Grade C2). Effective doses of DLI are associated with a significant risk of GVHD

11. Maintenance therapy

With the introduction of new agents, there is increasing interest in the role of maintenance therapy. No benefit has been demonstrated for the role of maintenance with chemotherapy (Belch *et al,* 1988; Drayson *et al,* 1998).

11.1. α-Interferon (IFN-α)

Many studies of IFN-α as maintenance have been carried out and have given conflicting results, but a meta-analysis of randomized trials (Fritz and Ludwig 2000) showed that although IFN-α results in moderate prolongation of PFS, the benefit in terms of OS is only minimal. In addition, IFN-α is associated with significant toxicity - in one trial more than one third of patients had to discontinue treatment due to side-effects (Schaar *et al,* 2005). This toxicity, the marginal benefits and the associated cost of long-term treatment have meant that IFN-α maintenance is no longer considered standard therapy.

11.2. Glucocorticoids

Corticosteroid maintenance was evaluated in 125 patients who were treated with either 50 mg or 10 mg of prednisolone on alternate days after induction therapy with VAD (Berenson *et al,* 2002). Therapy was continued until disease progression. EFS was significantly longer in the 50 mg group (14 vs. 5 months, p=0.003) as well as OS (37 vs. 26 months, p=0.05). This effect was not confirmed, however, in a multi-centre Canadian study, which randomized 292 patients to dexamethasone maintenance after induction treatment with either MP or M-Dex (Shustik *et al,* 2007). PFS was improved in the dexamethasone arm (2.8 years vs. 2.1 years, p=0.0002) but no difference in OS was observed. In addition, there were significantly more non-haematological toxicities reported in the

dexamethasone arm including hyperglycaemia (44% vs 27%) and infections (40% vs 27%). Currently, steroid maintenance is not recommended but trials of its use in combination with novel agents are ongoing.

11.3. Thalidomide

Several randomized prospective studies have investigated thalidomide as potential maintenance therapy post-ASCT and are summarized in Table 9 of Appendix 3. A recent meta-analysis assessed 4 randomized controlled trials investigating thalidomide maintenance (Hicks *et al,* 2008). An OS benefit in favour of thalidomide became apparent when the Barlogie trial (Barlogie *et al* 2006b) was excluded.

In the IFM-99 02 study, patients with deletion of chromosome 13 and patients who achieved at least a VGPR did not benefit from thalidomide maintenance (Attal *et al,* 2006). A dose finding study of thalidomide maintenance post-autograft showed significantly higher discontinuation rates due to toxicity at doses above 150 mg but no difference in EFS suggesting that lower doses are better tolerated but equally effective (Feyler *et al,* 2007). VTE was not significantly increased. In combination with prednisolone, lower doses of thalidomide (200 mg plus 50 mg prednisolone) are better tolerated than higher doses (400 mg plus 50 mg prednisolone) (Stewart *et al,* 2004). Long term treatment with thalidomide (>12 months) is associated with a very high incidence of peripheral neuropathy of approximately 75% (Tosi *et al,* 2005).

11.4 Bortezomib

Bortezomib in the maintenance setting has been shown to be beneficial following stem cell transplantation in a large phase III randomized study with superior response and PFS rates in the PAD arm compared to thalidomide in the VAD arm (Sonneveld *et al,* 2008). In elderly patients, bortezomib (in combination with either thalidomide or prednisolone) maintenance has been studied following induction therapy with either bortezomib, melphalan and prednisolone (VMP) or bortezomib, thalidomide and prednisolone (VTP) (Mateos *et al,* 2010). 178 patients were randomly assigned into either maintenance arm for up to 3 years. A complete remission rate of 42% was achieved after maintenance therapy (44% bortezomib plus thalidomide, 39% bortezomib plus prednisolone). This was an improvement of response rates after induction of 28% in the VTP group and 20% in the VMP group. After maintenance, no grade 3 haematological toxicities and low level peripheral neuropathy (2% bortezomib plus prednisolone, 7% bortezomib plus thalidomide) was detected. In another study of newly diagnosed elderly patients, maintenance with bortezomib plus thalidomide did not increase the response to induction with the 4-drug combination of VMP plus thalidomide (VMPT) (Boccadoro *et al,* 2010).

11.5 Lenalidomide

Given the toxicity of thalidomide, in particular peripheral neuropathy, lenalidomide would be an attractive alternative in the maintenance setting. In a phase III study, 614 patients age ≤ 65 years were randomized after ASCT to lenalidomide consolidation (25 mg on 21 days per month for 2 months) followed by lenalidomide maintenance (10-15 mg daily until relapse) or placebo (Attal *et al,* 2010). Maintenance with lenalidomide improved the 3-year PFS significantly, at 68% versus 35% with placebo with similar 2-year OS. Another phase III randomized study investigated maintenance lenalidomide 10 mg/day escalated to 15 mg/day after 3 months until disease progression in 418 patients age ≤70 years after ASCT (McCarthy *et al,* 2010) with significantly improved TTP (25.5 months in placebo arm vs. not reached in lenalidomide arm) after 12 months follow up. OS and adverse events were similar in both arms. Lenalidomide maintenance in elderly patients (age 65-75 years) after reduced dose ASCT (tandem 100 mg/m^2 melphalan) also resulted in improved CR rates (66% vs. 38% after ASCT) with acceptable toxicity in a phase II study of 102 patients (Palumbo *et al,* 2010).

Recommendations (*Grade C recommendation, level IV evidence unless stated)*

- IFN-α or single-agent corticosteroids cannot be routinely recommended as maintenance therapy (Grade A). In the allograft setting, IFN-α may be useful for patients who have not achieved a CR (Grade C2).
- Maintenance with single agent thalidomide therapy may improve EFS and OS in patients who did not achieve VGPR post high-dose therapy and in this setting maintenance therapy could be considered (Grade C2). Patients with deletion 13q may not benefit (Grade C2)
- The dose of thalidomide should not exceed 150 mg (grade B, level IIa recommendation) and no recommendation can be made with regards to the duration of thalidomide maintenance (Grade C2)
- In the maintenance setting, routine anticoagulant prophylaxis is not required. (Grade B1)
- At present, there is no evidence of benefit for the use of thalidomide maintenance in elderly patients who did not undergo autologous transplantation. (Grade C2)
- The combination of steroids and thalidomide is not recommended in the maintenance setting due to increase toxicity and unclear benefit over thalidomide alone. (Grade B1)
- Although promising data are emerging for the use of bortezomib or lenalidomide in the maintenance setting, long term published data are still awaited to be able to recommend their use outside clinical trials (Grade C2)

12. Management of relapsed myeloma including drugs in development

The introduction of a number of active anti-myeloma agents with mechanisms of action different from chemotherapy has increased the options available for patients in the relapse setting. Despite this, resistance usually develops over time. For most patients, the aims of treatment are similar to those at diagnosis - to achieve disease control, ameliorate symptoms, improve quality of life and prolong survival. However, for significant numbers of patients, the side-effects of treatment limit the choices available. Previously it was thought that early relapse carried a poor prognosis and that patients were likely to respond poorly to conventional chemotherapy but the introduction of thalidomide, bortezomib and lenalidomide has changed this.

Large data sets from randomized studies of traditional chemotherapy in relapsed patients do not exist. The largest randomized studies in this setting have employed the newer agents, and include the comparison of bortezomib against dexamethasone, and the comparison of lenalidomide and dexamethasone against dexamethasone alone (Richardson *et al,* 2005; Dimopoulos *et al,* 2007; Weber *et al,* 2007). Despite this lack of randomized data, some principles can be identified, based on published studies and UK experience, which may influence the choice of treatment at relapse. These include:

i. Re-exposure to the same treatment used at presentation is associated with increased rates of treatment resistance. Short remission duration with a given treatment is a strong indicator to employ an alternative regimen

ii. Single agent activity of the novel agents is limited and these agents should normally be given in combination to maximize benefit

Because of disease heterogeneity and variability in patient-specific factors including co-morbidities and the persistence of toxicities related to previous therapy, there can be no standard approach recommended for the treatment at relapse. However, some of the evidence informing recommendations for the treatment of relapsed myeloma in the UK is summarized below.

12.1 Use of novel agents at relapse

The 3 agents most often used in treating relapsed patients are thalidomide, bortezomib and lenalidomide. They are generally used in combination with corticosteroids (pulsed or weekly dexamethasone), and sometimes an alkylating agent, most commonly cyclophosphamide. The evidence for efficacy and issues relating to toxicity for each are summarized below.

Thalidomide

Numerous studies have confirmed the efficacy of thalidomide in the relapsed and refractory setting with a response rate of 30-40% when used alone (Barlogie *et al,* 2001) and 60% when used in combination with dexamethasone (Dimopoulos *et al,* 2001; Palumbo *et al,* 2001). Synergy has been further demonstrated by the observation that when thalidomide is combined with dexamethasone in patients documented to be refractory to both drugs given separately (not necessarily sequentially) up to 25% of patients will respond to the combination (Weber *et al*, 1999). The response rate is

increased further by the addition of chemotherapy. Numerous combinations of thalidomide with cytotoxic chemotherapy in addition to dexamethasone have also been explored resulting in improved response rates compared with the single agent. The most frequently used combination in the UK is CTD with reported response rates of up to 80% (Dimopoulos *et al,* 2004; Garcia-Sanz *et al,* 2004; Kropff *et al,* 2003; Kyriakou *et al,* 2005; Sidra *et al,* 2006).

Response to therapy is rapid with responding patients showing a decline in their M-protein in the first 28 days, although the maximal response occurs considerably later than this (Waage *et al,* 2004). The optimal dose remains unclear. Although in the original studies the target dose was 800 mg/day this is rarely achievable and in a meta-analysis the median tolerated dose was 400 mg/day (Glasmacher *et al,* 2006). The optimal duration of therapy has also not been defined. To date most studies have dosed until progression or adverse events required discontinuation; in the CTD regimen a maximum of 6 courses is usually given although in the relapse setting it is common for thalidomide alone to be continued after completion.

Bortezomib

Bortezomib has US Food and Drug Administration (FDA) and European Union (EU) licensing for patients with relapsed myeloma and NICE approval as monotherapy for patients at first relapse. In a phase III study, 669 patients with relapsed myeloma were randomized to either bortezomib or high dose dexamethasone (Richardson *et al,* 2005), bortezomib demonstrated superiority with an updated response rate of 42% compared to 18% in the dexamethasone group ($P<0.001$) and an advantage in both TTP (median 6.22 months vs 3.49 months, $p<0.001$) and OS ($p< 0.001$) (Richardson *et al,* 2007) despite more than 60% cross-over to bortezomib from the dexamethasone arm. In addition, 56% of patients improved their initial response with continued therapy, suggesting a potential role for extended therapy.

Phase II data indicate improvement in response when dexamethasone is added in patients with a sub-optimal response to bortezomib alone (Richardson *et al,* 2003). This is consistent with in vitro data of additive cytotoxicity (Hideshima *et al,* 2001) and provides the rationale for the use of bortezomib with dexamethasone at the commencement of therapy. In these studies, bortezomib was administered twice a week by intravenous bolus for two weeks of a 21-day cycle up to a maximum of 8 cycles, although the majority of responses occurred within three cycles. Dexamethasone was given at 20 mg on the day of and the day after each bortezomib dose.

Many studies combining bortezomib with chemotherapeutic or other novel agents have also been performed in the relapsed setting. A large phase III study comparing bortezomib and liposomal doxorubicin to bortezomib alone demonstrated superior response rates and response duration for the combination (Orlowski *et al,* 2007). Data from numerous phase II trials demonstrate other

combination approaches to be safe with higher response rates than with single agents. However, longer follow up and data from randomized phase III studies are awaited.

Lenalidomide

In the EU, lenalidomide is licensed in combination with dexamethasone for the treatment of myeloma patients who have received at least one prior therapy and, in the UK, recent National Institute of Clinical Excellence (NICE) guidance has approved the drug also in combination with dexamethasone for the treatment of patients at second or greater relapse.

Lenalidomide is given at a dose of 25 mg/day orally for 21 days out of a 28-day cycle (Richardson *et al,* 2002) with dexamethasone initially with three 40 mg/day for 4 day pulses per cycle, reducing to a single pulse in subsequent cycles. Two phase III randomized, multi-centre, double-blind, placebo-controlled studies using identical protocols have been carried out comparing its use to dexamethasone alone (results summarized in (Dimopoulos *et al,* 2009a)). Results of the studies were similar, showing significantly higher overall response rates in the lenalidomide/dexamethasone group compared to the control group (60.6% versus 21.9%, $p<0.001$). At a median follow up of 48 months, a pooled analysis of the 2 trials showed TTP and OS were also significantly longer in the lenalidomide/dexamethasone group despite the fact that patients in the dexamethasone only arm were allowed to receive lenalidomide treatment at relapse, and following the early unblinding of these 2 studies, patients randomized to dexamethasone alone were offered lenalidomide (Dimopoulos *et al,* 2009a).

Further analysis of these phase III trial results suggests that higher response rates and improved TTP is achieved in patients treated at first relapse, compared to those treated at subsequent relapse (65% versus 58% and 71 weeks versus 41 weeks respectively), although the outcomes for patients treated later in their disease course were still significantly higher in the lenalidomide/dexamethasone arms (Stadtmauer *et al,* 2009). Patients who had been exposed to thalidomide also benefited from lenalidomide (54% response rate vs 15% in the dexamethasone arm) although response rates were slightly lower compared to patients who had not been previously exposed to thalidomide (63% and 27% for lenalidomide/dexamethasone and dexamethasone respectively) *(Wang et al, 2006)*. Grade 3 or 4 neutropenia or thrombocytopenia occurred in 35% and 13%, respectively, in patients receiving lenalidomide and dexamethasone for relapsed myeloma (Dimopoulos *et al,* 2009a).

12.2 Transplantation at relapse

High dose therapy and stem cell transplantation may be considered in patients who have not had a prior stem cell transplant (Fermand *et al,* 1998). A second transplant can also be an effective strategy in selected patients who relapse more than 18 months after an initial autograft and this is currently under investigation in a randomized trial in the UK. This is discussed in more detail in section 9.4.

12.3 Combinations of novel agents and newer anti-myeloma therapies

Ongoing phase II and III studies are comparing combinations of the above agents as therapy both at relapse and in the front line setting. Initial results are very promising and suggest that combinations of lenalidomide, bortezomib and dexamethasone, and bortezomib, thalidomide and dexamethasone are well tolerated and give high response rates.

12.4 Drugs in development

Many new drugs are in development. Promising results in early trials have been reported with several drugs including second and third generation immunomodulatory drugs, such as pomalidomide (Lacy et al, 2009), proteasome inhibitors including carfilzomib (O'Connor et al, 2009) and alkylating agents such as bendamustine (Pönisch et al, 2008). High response rates have been reported with good side-effect profiles, although the studies are too early to comment on any survival benefits.

In addition, the safety and efficacy of a number of novel anti-myeloma therapies is currently being explored in clinical trials, either as single agents or in combination with more traditional chemotherapeutics. Examples include target-specific compounds such as AKT, fibroblast growth factor receptor 3 and interleukin-6 inhibitors, heat shock protein 90 inhibitors and chromatin structure modifiying agents, such as histone deacetylase inhibitors and demethylating agents. Pre-clinical *in-vitro* and *in-vivo* studies are encouraging but there is currently not enough clinical evidence to support their use outside of clinical trials.

12.5 Local radiotherapy

Some patients may relapse with local disease, eg. spinal plasmacytoma, with little evidence of active disease elsewhere. Such patients, especially if they are beyond first relapse, may be treated with local radiotherapy, avoiding the additional toxicity of systemic therapy, which would be an option for subsequent disease re-activation.

12.6 Choice of treatment at relapse

Decisions regarding treatment at relapse should be made according to a number of factors including the timing of relapse, efficacy and toxicity of drugs used in prior therapy (eg peripheral neuropathy), age, BM and renal function, co-morbidities (eg. diabetes) and patient preference. A suggested algorithm (see Appendix 5) takes these factors into account and provides broad guidance but it should be noted that the evidence for recommending one treatment over another at specific time points does not always exist. Despite this, there are a number of common treatment pathways developed in the UK on the background of trial evidence, experience and NICE approvals. As far as possible, treatment should be individualized and it should be recognized that it is not necessarily

best practice to mandate particular therapies at specified time points. In the future, it is likely that therapy will be 'risk-adapted' and the presence or absence of specific prognostic factors may determine choice of therapy (reviewed in (San Miguel *et al,* 2008a)) both at diagnosis and relapse. Entry into clinical trials should be considered at each relapse.

Many patients in the UK will receive a thalidomide-based therapy at induction +/- HDT/ASCT. It is recommended that these patients should be considered for bortezomib +/- steroids and/or chemotherapy at first relapse. For some, this will not be considered the best therapy eg. patients with pre-existing neuropathy, immobility, lack of venous access, or patient choice. Patients who have enjoyed a long first plateau phase (>18 months) following their initial therapy, and are unsuitable for bortezomib may be treated with the same regimen. Many patients will have responded to thalidomide as their initial therapy, and such patients are likely to respond again at relapse. The use of a second ASCT is discussed below and in Section 9.4.

Patients at second and subsequent relapse, or patients at first relapse intolerant of thalidomide or bortezomib should be considered for lenalidomide. Patients presenting in renal failure should be treated on a bortezomib-containing regimen, to achieve rapid reduction in light chain load to the kidneys, and maximize chances of regaining renal function.

Recommendations

- The most appropriate management should be determined on an individual basis depending on the timing of relapse, age, prior therapy, BM function and co-morbidities, and patient preference (Grade A1)
- Extensive trial data support the use of thalidomide, bortezomib and lenalidomide-based regimens as treatment modalities at first and subsequent relapse (Grade A1)
- Clinical effectiveness of thalidomide, bortezomib and lenalidomide is not dependent on the number of previous lines of therapy, or type of therapy previously received. (Grade C2)
- Unless contraindicated, treatment with thalidomide, bortezomib or lenalidomide treatment should be delivered with dexamethasone +/- chemotherapy to increase the response rate. (Grade A1)
- A second ASCT may be considered in patients who had a good response to the initial transplant procedure (≥ 18 months to disease progression)(Grade B1)
- Where possible, patients should be treated in the context of a clinical trial. Phase I/II trials are appropriate for patients with relapsed/refractory myeloma (Grade A1)
- Good supportive therapy is essential (Grade A1)

13. Patient Information and Support

Provision of information and support for patients and their carers is essential if a patient is to come to terms with their diagnosis and make informed decisions about treatment options. It will also enable them to understand the importance of compliance with treatment regimens that can be demanding. Myeloma is an individual cancer affecting patients and their carers in many physical, emotional and social ways. Therefore, information and support should, if possible, be tailored to individual needs.

As a minimum, it is important for patients and their families to understand the disease and the aims and risks of treatment and that, although treatment is not curative, it will relieve symptoms, prolong survival and improve quality of life; the positive aspects of treatment need to be stressed. They should be aware that their treatment and care will have been discussed and agreed by an MDT and should be given the details of key workers. Patients should be told about appropriate clinical studies and be given a sufficient level of information and time to make an informed decision as to whether to take part or not. Patients with myeloma should be aware of support networks in the community; the specialist team should provide patients and their families with information on local support networks, whether these are specific to myeloma or in relation to cancer generally.

Finally, the symptoms of myeloma and the side-effects of treatment may result in long-term disability and preclude many patients from returning to work. High-dose and conventional chemotherapy regimens also make employment impractical for periods of several months. Patients commonly need advice on socio-economic problems resulting from the condition and its treatment. The specialist team needs to be able to provide information on state benefits, e.g. Disability Living Allowance, and other appropriate social services.

Key recommendations

- The diagnosis needs to be communicated honestly to the patient and their family without delay
- Information should be communicated in a quiet area with privacy, ideally in the company of a close relative and with the presence of a specialist nurse. The information needs of the patient's family need to be facilitated wherever possible
- Patients and their partners / carers should be given time to ask appropriate questions once they have been given the diagnosis; this may be best be done after an interval of a few hours or days
- Patients should be made aware of appropriate clinical studies
- Treatment plans need to be communicated simply to the patient and his / her carer and should be clearly written in the case record so that the information is readily accessible to other members of the multi-disciplinary specialist team
- Patients need to be informed of the names of the key members of the specialist team who are in charge of their care and given clear information on access to advice/support from the team

- At the end of a consultation it is recommended that patients and their family / carers have written information on the condition. It should also guide patients and their family / carers on access to other information services.

Useful information sources

Myeloma UK provides information and support to all those affected by myeloma and aims to improve treatment and care through education, research, campaigning and awareness. www.myeloma.org.uk

Leukaemia and lymphoma Research supports research in myeloma and also provides patient information booklets. www.llresearch.org.uk

Macmilllan cancer support provides practical, medical and financial support to patients www.macmillan.org.uk

References

Aitchison, R.G., Reilly, I.A., Morgan, A.G. & Russell, N.H. (1990) Vincristine, adriamycin and high dose steroids in myeloma complicated by renal failure. *British Journal of Cancer,* **61,** 765-766.

Al-Quran, S.Z., Yang, L., Magill, J.M., Braylan, R.C. & Douglas-Nikitin, V.K. (2007) Assessment of bone marrow plasma cell infiltrates in multiple myeloma: the added value of CD138 immunohistochemistry. *Human Pathololgy,* **38,** 1779-1787.

Alexanian, R., Barlogie, B. & Tucker, S. (1990) VAD-based regimens as primary treatment for multiple myeloma. *American Journal of Hematology,* **33,** 86-89.

Alexanian, R., Dimopoulos, M.A., Delasalle, K. & Barlogie, B. (1992) Primary dexamethasone treatment of multiple myeloma. *Blood,* **80,** 887-890.

Alexanian, R., Dimopoulos, M., Hester, J., Delasalle, K. & Champlin, R. (1994a) Early myeloablative therapy for multiple myeloma. *Blood,* **84,** 4278-4282.

Alexanian, R., Dimopoulos, M., Smith, T., Delasalle, K., Barlogie, B. & Champlin, R. (1994b) Limited value of myeloablative therapy for late multiple myeloma. *Blood,* **83,** 512-516.

Anderson, K.C. (2006) Advances in drug development: New drugs for multiple myeloma. *Clinical Advances in Hematology and Oncology,* **4,** 592-594.

Attal, M., Harousseau, J.L., Stoppa, A.M., Sotto, J.J., Fuzibet, J.G., Rossi, J.F., Casassus, P., Maisonneuve, H., Facon, T., Ifrah, N., Payen, C. & Bataille, R. (1996) A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. *New England Journal of Medicine,* **335,** 91-97.

Attal, M., Harousseau, J.L., Facon, T., Guilhot, F., Doyen, C., Fuzibet, J.G., Monconduit, M., Hulin, C., Caillot, D., Bouabdallah, R., Voillat, L., Sotto, J.J., Grosbois, B. & Bataille, R. (2003) Single versus double autologous stem-cell transplantation for multiple myeloma. *New England Journal of Medicine,* **349,** 2495-2502.

Attal, M., Harousseau, J.L., Leyvraz, S., Doyen, C., Hulin, C., Benboubker, L., Yakoub Agha, I., Bourhis, J.H., Garderet, L., Pegourie, B., Dumontet, C., Renaud, M., Voillat, L., Berthou, C., Marit, G., Monconduit, M., Caillot, D., Grobois, B., Avet-Loiseau, H.,

Moreau, P. & Facon, T. (2006) Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood,* **108,** 3289-3294.
Attal, M., Cristini, C., Marit, G., Caillot, D., Facon, T., Hullin, C., Moreau, P., Mathiot, C., Avet-Loiseau, H. & Harousseau, J.L. (2010) Lenalidomide maintenance after transplantation for myeloma. *Journal of Clinical Oncology,* **28,** 15s (abstract 8018).
Augustson, B.M., Begum, G., Dunn, J.A., Barth, N.J., Davies, F., Morgan, G., Behrens, J., Smith, A., Child, J.A. & Drayson, M.T. (2005) Early mortality after diagnosis of multiple myeloma: analysis of patients entered onto the United kingdom Medical Research Council trials between 1980 and 2002--Medical Research Council Adult Leukaemia Working Party. *Journal of Clinical Oncology,* **23,** 9219-9226.
Avet-Loiseau, H., Garand, R., Lode, L., Robillard, N. & Bataille, R. (2003a) 14q32 Translocations discriminate IgM multiple myeloma from Waldenstrom's macroglobulinemia. *Seminars in Oncology,* **30,** 153-155.
Avet-Loiseau, H., Garand, R., Lode, L., Harousseau, J.L. & Bataille, R. (2003b) Translocation t(11;14)(q13;q32) is the hallmark of IgM, IgE, and nonsecretory multiple myeloma variants. *Blood,* **101,** 1570-1571.
Avet-Loiseau, H., Moreau, P., Mathiot, C., Charbonnel, C., Caillot, D., Facon, T., Attal, M., Benboubker, L., Hulin, C., Marit, G., Minvielle, S. & Harousseau, J.-L. (2009) Induction with velcade/dexamethasone partially overcomes the poor prognosis of t(4;14), but not that of del(17p), in young patients with multiple myeloma. . *Blood (ASH Annual Meeting Abstracts),* **114,** Abstract 957.
Badros, A., Barlogie, B., Siegel, E., Morris, C., Desikan, R., Zangari, M., Fassas, A., Anaissie, E., Munshi, N. & Tricot, G. (2001a) Autologous stem cell transplantation in elderly multiple myeloma patients over the age of 70 years. *British Journal of Haematology,* **114,** 600-607.
Badros, A., Barlogie, B., Siegel, E., Roberts, J., Langmaid, C., Zangari, M., Desikan, R., Shaver, M.J., Fassas, A., McConnell, S., Muwalla, F., Barri, Y., Anaissie, E., Munshi, N. & Tricot, G. (2001b) Results of autologous stem cell transplant in multiple myeloma patients with renal failure. *British Journal of Haematology,* **114,** 822-829.
Barlogie, B., Jagannath, S., Vesole, D.H., Naucke, S., Cheson, B., Mattox, S., Bracy, D., Salmon, S., Jacobson, J., Crowley, J. & Tricot, G. (1997) Superiority of tandem autologous transplantation over standard therapy for previously untreated multiple myeloma. *Blood,* **89,** 789-793.
Barlogie, B., Desikan, R., Eddlemon, P., Spencer, T., Zeldis, J., Munshi, N., Badros, A., Zangari, M., Anaissie, E., Epstein, J., Shaughnessy, J., Ayers, D., Spoon, D. & Tricot, G. (2001) Extended survival in advanced and refractory multiple myeloma after single-agent thalidomide: identification of prognostic factors in a phase 2 study of 169 patients. *Blood,* **98,** 492-494.
Barlogie, B., Kyle, R.A., Anderson, K.C., Greipp, P.R., Lazarus, H.M., Hurd, D.D., McCoy, J., Moore, D.F., Jr., Dakhil, S.R., Lanier, K.S., Chapman, R.A., Cromer, J.N., Salmon, S.E., Durie, B. & Crowley, J.C. (2006a) Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321. *Journal of Clinical Oncology,* **24,** 929-936.
Barlogie, B., Tricot, G., Anaissie, E., Shaughnessy, J., Rasmussen, E., van Rhee, F., Fassas, A., Zangari, M., Hollmig, K., Pineda-Roman, M., Lee, C., Talamo, G., Thertulien, R., Kiwan, E., Krishna, S., Fox, M. & Crowley, J. (2006b) Thalidomide and hematopoietic-cell transplantation for multiple myeloma. *New England Journal of Medicine,* **354,** 1021-1030.
Barri, Y.M., Munshi, N.C., Sukumalchantra, S., Abulezz, S.R., Bonsib, S.M., Wallach, J. & Walker, P.D. (2004) Podocyte injury associated glomerulopathies induced by pamidronate. *Kidney International,* **65,** 634-641.

Belch, A., Shelley, W., Bergsagel, D., Wilson, K., Klimo, P., White, D. & Willan, A. (1988) A randomized trial of maintenance versus no maintenance melphalan and prednisone in responding multiple myeloma patients. *British Journal of Cancer,* **57,** 94-99.

Belch, A.R., Bergsagel, D.E., Wilson, K., O'Reilly, S., Wilson, J., Sutton, D., Pater, J., Johnston, D. & Zee, B. (1991) Effect of daily etidronate on the osteolysis of multiple myeloma. *Journal of Clinical Oncology,* **9,** 1397-1402.

Benson, D.M., Jr., Elder, P.J., Lin, T.S., Blum, W., Penza, S., Avalos, B., Copelan, E. & Farag, S.S. (2007) High-dose melphalan versus busulfan, cyclophosphamide, and etoposide as preparative regimens for autologous stem cell transplantation in patients with multiple myeloma. *Leukemia Research,* **31,** 1069-1075.

Berenson, J.R., Lichtenstein, A., Porter, L., Dimopoulos, M.A., Bordoni, R., George, S., Lipton, A., Keller, A., Ballester, O., Kovacs, M., Blacklock, H., Bell, R., Simeone, J.F., Reitsma, D.J., Heffernan, M., Seaman, J. & Knight, R.D. (1998) Long-term pamidronate treatment of advanced multiple myeloma patients reduces skeletal events. Myeloma Aredia Study Group. *Journal of Clinical Oncology,* **16,** 593-602.

Berenson, J.R., Rosen, L.S., Howell, A., Porter, L., Coleman, R.E., Morley, W., Dreicer, R., Kuross, S.A., Lipton, A. & Seaman, J.J. (2001) Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases. *Cancer,* **91,** 1191-1200.

Berenson, J.R., Crowley, J.J., Grogan, T.M., Zangmeister, J., Briggs, A.D., Mills, G.M., Barlogie, B. & Salmon, S.E. (2002) Maintenance therapy with alternate-day prednisone improves survival in multiple myeloma patients. *Blood,* **99,** 3163-3168.

Bird, J.M., Fuge, R., Sirohi, B., Apperley, J.F., Hunter, A., Snowden, J., Mahendra, P., Milligan, D., Byrne, J., Littlewood, T., Fegan, C., McQuaker, G., Pagliuca, A., Johnson, P., Rahemtulla, A., Morris, C. & Marks, D.I. (2006) The clinical outcome and toxicity of high-dose chemotherapy and autologous stem cell transplantation in patients with myeloma or amyloid and severe renal impairment: a British Society of Blood and Marrow Transplantation study. *British Journal of Haematology,* **134,** 385-390.

Bird, J., Behrens, J., Westin, J., Turesson, I., Drayson, M., Beetham, R., D'Sa, S., Soutar, R., Waage, A., Gulbrandsen, N., Gregersen, H. & Low, E. (2009) UK Myeloma Forum (UKMF) and Nordic Myeloma Study Group (NMSG): guidelines for the investigation of newly detected M-proteins and the management of monoclonal gammopathy of undetermined significance (MGUS). *British Journal of Haematology,* **147,** 22-42.

Bjorkstrand, B., Lacobelli, S. & Hegenbart, A. (2009) Autologous stem cell transplantation (ASCT) versus ASCT followed by reduced-intensity conditioning (RIC) allogeneic SCT with identical sibling donor in previously untreated multiple myeloma (MM): a prospective controlled trial by the EBMT. *Bone Marrow Transplantation (abstract),* **43,** 223.

Blade, J. & Kyle, R.A. (1994) IgD monoclonal gammopathy with long-term follow-up. *British Journal of Haematology,* **88,** 395-396.

Blade, J., Samson, D., Reece, D., Apperley, J., Bjorkstrand, B., Gahrton, G., Gertz, M., Giralt, S., Jagannath, S. & Vesole, D. (1998) Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. *British Journal of Haematology,* **102,** 1115-1123.

Blade, J., San Miguel, J.F., Fontanillas, M., Esteve, J., Maldonado, J., Alcala, A., Brunet, S., Garcia-Conde, J., Besalduch, J., Moro, M.J., Fernandez-Calvo, J., Conde, E., Font, L., Gardella, S., Carnero, M., Carbonell, F., Marti, J.M., Hernandez-Martin, J., Ortega, F., Besses, C., Ribera, J.M., Trujillo, J., Escudero, M.L., Rozman, C., Estape, J. & Montserrat, E. (2001) Increased conventional chemotherapy does not improve survival in multiple myeloma: long-term results of two PETHEMA trials including 914 patients. *Hematology Journal,* **2,** 272-278.

Boccadoro, M., Bringhen, S., Gaidano, G., Ria, R., Offidani, M., Patriarca, F., Nozzoli, C., Musto, P., Petrucci, M. & Palumbo, A.P. (2010) Bortezomib, melphalan, prednisone, and thalidomide (VMPT) followed by maintenance with bortezomib and thalidomide (VT) for initial treatment of elderly multiple myeloma patients. *Journal of Clinical Oncology,* **28,** 15s (abstract 8013).

Bradwell, A.R., Carr-Smith, H.D., Mead, G.P., Harvey, T.C. & Drayson, M.T. (2003) Serum test for assessment of patients with Bence Jones myeloma. *Lancet,* **361,** 489-491.

Brenner, H., Gondos, A. & Pulte, D. (2009) Expected long-term survival of patients diagnosed with multiple myeloma in 2006-2010. *Haematologica,* **94,** 270-275.

Bruno, B., Rotta, M., Patriarca, F., Mordini, N., Allione, B., Carnevale-Schianca, F., Giaccone, L., Sorasio, R., Omede, P., Baldi, I., Bringhen, S., Massaia, M., Aglietta, M., Levis, A., Gallamini, A., Fanin, R., Palumbo, A., Storb, R., Ciccone, G. & Boccadoro, M. (2007) A comparison of allografting with autografting for newly diagnosed myeloma. *New England Journal of Medicine,* **356,** 1110-1120.

Capria, S., Petrucci, M.T., Pulsoni, A., Ribersani, M., Baldacci, E., de Propris, M.S. & Meloni, G. (2006) High-dose idarubicin, busulphan and melphalan for autologous stem cell transplantation in multiple myeloma responsive to DAV chemotherapy: comparison with a historical control. *Acta Haematologica,* **115,** 9-14.

Carlson, K., Hjorth, M. & Knudsen, L.M. (2005) Toxicity in standard melphalan-prednisone therapy among myeloma patients with renal failure--a retrospective analysis and recommendations for dose adjustment. *British Journal of Haematology,* **128,** 631-635.

Cavo, M., Zamagni, E., Tosi, P., Tacchetti, P., Cellini, C., Cangini, D., de Vivo, A., Testoni, N., Nicci, C., Terragna, C., Grafone, T., Perrone, G., Ceccolini, M., Tura, S. & Baccarani, M. (2005) Superiority of thalidomide and dexamethasone over vincristine-doxorubicindexamethasone (VAD) as primary therapy in preparation for autologous transplantation for multiple myeloma. *Blood,* **106,** 35-39.

Cavo, M., Tosi, P., Zamagni, E., Cellini, C., Tacchetti, P., Patriarca, F., Di Raimondo, F., Volpe, E., Ronconi, S., Cangini, D., Narni, F., Carubelli, A., Masini, L., Catalano, L., Fiacchini, M., de Vivo, A., Gozzetti, A., Lazzaro, A., Tura, S. & Baccarani, M. (2007) Prospective, randomized study of single compared with double autologous stem-cell transplantation for multiple myeloma: Bologna 96 clinical study. *Journal of Clinical Oncology,* **25,** 2434-2441.

Cavo, M., Tacchetti, P., Patriarca, F., Petrucci, M.T., Pantani, L., Galli, M., Raimondo, F.D., Crippa, C., Bringhen, S., Offidani, M., Narni, F., Montefusco, V., Zamagni, E., Spadano, T., Pescosta, N., Baldini, L., Cellini, C., Caravita, T., Ledda, A., Falcone, A., Tosi, P., Nozzoli, C., Zambello, R., Masini, L., Agostini, P., Fiacchini, M. & Baccarani, M. (2009) A phase III study of double autotransplantation incorporating bortezomib-thalidomide-dexamethasone (VTD) or thalidomide-dexamethasone (TD) for multiple myeloma: superior clinical outcomes with VTD compared to TD. *Blood (ASH Annual Meeting Abstracts),* **114,** Abstract 351.

Chanan-Khan, A.A., Kaufman, J.L., Mehta, J., Richardson, P.G., Miller, K.C., Lonial, S., Munshi, N.C., Schlossman, R., Tariman, J. & Singhal, S. (2007) Activity and safety of bortezomib in multiple myeloma patients with advanced renal failure: a multicenter retrospective study. *Blood,* **109,** 2604-2606.

Chang, J.T., Green, L. & Beitz, J. (2003) Renal failure with the use of zoledronic acid. *New England Journal of Medicine,* **349,** 1676-1679.

Chen, N., Lau, H., Kong, L., Kumar, G., Zeldis, J.B., Knight, R. & Laskin, O.L. (2007) Pharmacokinetics of lenalidomide in subjects with various degrees of renal impairment and in subjects on hemodialysis. *The Journal of Clinical Pharmacology,* **47,** 1466-1475.

Child, J.A., Morgan, G.J., Davies, F.E., Owen, R.G., Bell, S.E., Hawkins, K., Brown, J., Drayson, M.T. & Selby, P.J. (2003) High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *New England Journal of Medicine,* **348,** 1875-1883.

Clark, A.D., Shetty, A. & Soutar, R. (1999) Renal failure and multiple myeloma: pathogenesis and treatment of renal failure and management of underlying myeloma. *Blood Reviews,* **13,** 79-90.

Clark, W.F., Stewart, A.K., Rock, G.A., Sternbach, M., Sutton, D.M., Barrett, B.J., Heidenheim, A.P., Garg, A.X. & Churchill, D.N. (2005) Plasma exchange when myeloma presents as acute renal failure: a randomized, controlled trial. *Annals of Internal Medicine,* **143,** 777-784.

Cocks, K., Cohen, D., Wisloff, F., Sezer, O., Lee, S., Hippe, E., Gimsing, P., Turesson, I., Hajek, R., Smith, A., Graham, L., Phillips, A., Stead, M., Velikova, G. & Brown, J. (2007) An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-MY20) in assessing the quality of life of patients with multiple myeloma. *European Journal of Cancer,* **43,** 1670-1678.

Coleman, R.E. (1997) Skeletal complications of malignancy. *Cancer,* **80,** 1588-1594.

Corradini, P., Cavo, M., Lokhorst, H., Martinelli, G., Terragna, C., Majolino, I., Valagussa, P., Boccadoro, M., Samson, D., Bacigalupo, A., Russell, N., Montefusco, V., Voena, C. & Gahrton, G. (2003) Molecular remission after myeloablative allogeneic stem cell transplantation predicts a better relapse-free survival in patients with multiple myeloma. *Blood,* **102,** 1927-1929.

Corral, L.G. & Kaplan, G. (1999) Immunomodulation by thalidomide and thalidomide analogues. *Annals of the Rheumatic Diseases,* **58 Suppl 1,** 1107-1113.

Crawley, C., Iacobelli, S., Bjorkstrand, B., Apperley, J.F., Niederwieser, D. & Gahrton, G. (2007) Reduced-intensity conditioning for myeloma: lower nonrelapse mortality but higher relapse rates compared with myeloablative conditioning. *Blood,* **109,** 3588-3594.

Crawley, C., Lalancette, M., Szydlo, R., Gilleece, M., Peggs, K., Mackinnon, S., Juliusson, G., Ahlberg, L., Nagler, A., Shimoni, A., Sureda, A., Boiron, J.M., Einsele, H., Chopra, R., Carella, A., Cavenagh, J., Gratwohl, A., Garban, F., Zander, A., Bjorkstrand, B., Niederwieser, D., Gahrton, G. & Apperley, J.F. (2005) Outcomes for reduced-intensity allogeneic transplantation for multiple myeloma: an analysis of prognostic factors from the Chronic Leukaemia Working Party of the EBMT. *Blood,* **105,** 4532-4539.

Croucher, P.I. & Apperley, J.F. (1998) Bone disease in multiple myeloma. *British Journal of Haematology,* **103,** 902-910.

D'Sa, S., Yong, K., Kyriakou, C., Bhattacharya, S., Peggs, K.S., Foulkes, B., Watts, M.J., Ings, S.J., Ardeshna, K.M., Goldstone, A.H. & Williams, C.D. (2004) Etoposide, methylprednisolone, cytarabine and cisplatin successfully cytoreduces resistant myeloma patients and mobilizes them for transplant without adverse effects. *British Journal of Haematology,* **125,** 756-765.

D'Sa, S., Abildgaard, N., Tighe, J., Shaw, P. & Hall-Craggs, M. (2007) Guidelines for the use of imaging in the management of myeloma. *British Journal of Haematology,* **137,** 49-63.

Davies, F.E., Forsyth, P.D., Rawstron, A.C., Owen, R.G., Pratt, G., Evans, P.A., Richards, S.J., Drayson, M., Smith, G.M., Selby, P.J., Child, J.A. & Morgan, G.J. (2001) The impact of attaining a minimal disease state after high-dose melphalan and autologous transplantation for multiple myeloma. *British Journal of Haematology,* **112,** 814-819.

De Rosa, L., Anghel, G., Pandolfi, A., Riccardi, M., Amodeo, R. & Majolino, I. (2004) Hemopoietic recovery and infectious complications in breast cancer and multiple myeloma after autologous CD34+ cell-selected peripheral blood progenitor cell transplantation. *International Journal of Hematology,* **79,** 85-91.

Dimopoulos, M.A., Palumbo, A., Delasalle, K.B. & Alexanian, R. (1994) Primary plasma cell leukaemia. *British Journal of Haematology,* **88,** 754-759.

Dimopoulos, M.A., Zervas, K., Kouvatseas, G., Galani, E., Grigoraki, V., Kiamouris, C., Vervessou, E., Samantas, E., Papadimitriou, C., Economou, O., Gika, D., Panayiotidis, P., Christakis, I. & Anagnostopoulos, N. (2001) Thalidomide and dexamethasone combination for refractory multiple myeloma. *Annals of Oncology,* **12,** 991-995.

Dimopoulos, M.A., Hamilos, G., Zomas, A., Gika, D., Efstathiou, E., Grigoraki, V., Poziopoulos, C., Xilouri, I., Zorzou, M.P., Anagnostopoulos, N. & Anagnostopoulos, A. (2004) Pulsed cyclophosphamide, thalidomide and dexamethasone: an oral regimen for previously treated patients with multiple myeloma. *Hematology Journal,* **5,** 112-117.

Dimopoulos, M., Spencer, A., Attal, M., Prince, H.M., Harousseau, J.L., Dmoszynska, A., San Miguel, J., Hellmann, A., Facon, T., Foà, R., Corso, A., Masliak, Z., Olesnyckyj, M., Yu, Z., Patin, J., Zeldis, J.B. & Knight, R.D. (2007) Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *New England Journal of Medicine,* **357,** 2123-2132.

Dimopoulos, M.A., Chen, C., Spencer, A., Niesvizky, R., Attal, M., Stadtmauer, E.A., Petrucci, M.T., Yu, Z., Olesnyckyj, M., Zeldis, J.B., Knight, R.D. & Weber, D.M. (2009a) Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. *Leukemia,* **23,** 2147-2152.

Dimopoulos, M.A., Richardson, P.G., Schlag, R., Khuageva, N.K., Shpilberg, O., Kastritis, E., Kropff, M., Petrucci, M.T., Delforge, M., Alexeeva, J., Schots, R., Masszi, T., Mateos, M.V., Deraedt, W., Liu, K., Cakana, A., van de Velde, H. & San Miguel, J.F. (2009b) VMP (Bortezomib, Melphalan, and Prednisone) is active and well tolerated in newly diagnosed patients with multiple myeloma with moderately impaired renal function, and results in reversal of renal impairment: cohort analysis of the phase III VISTA study. *Journal of Clinical Oncology,* **27,** 6086-6093.

Dispenzieri, A., Kyle, R.A., Katzmann, J.A., Therneau, T.M., Larson, D., Benson, J., Clark, R.J., Melton, L.J., 3rd, Gertz, M.A., Kumar, S.K., Fonseca, R., Jelinek, D.F. & Rajkumar, S.V. (2008) Immunoglobulin free light chain ratio is an independent risk factor for progression of smoldering (asymptomatic) multiple myeloma. *Blood,* **111,** 785-789.

Djulbegovic, B., Wheatley, K., Ross, J., Clark, O., Bos, G., Goldschmidt, H., Cremer, F., Alsina, M. & Glasmacher, A. (2002) Bisphosphonates in multiple myeloma. *Cochrane Database Systemic Reviews,* **3,** CD003188.

Drake, M.B., Iacobelli, S., van Biezen A., Morris C., Apperley J.F., Niederwieser D., Björkstrand B., Gahrton G.; European Group for Blood and Marrow Transplantation and the European Leukemia Net. (2010) Primary plasma cell leukemia and autologous stem cell transplantation. *Haematologica*, **95**: 804-9

Drayson, M.T., Chapman, C.E., Dunn, J.A., Olujohungbe, A.B. & Maclennan, I.C. (1998) MRC trial of alpha2b-interferon maintenance therapy in first plateau phase of multiple myeloma. MRC Working Party on Leukaemia in Adults. *British Journal of Haematology,* **101,** 195-202.

Drayson, M., Tang, L.X., Drew, R., Mead, G.P., Carr-Smith, H. & Bradwell, A.R. (2001) Serum free light-chain measurements for identifying and monitoring patients with nonsecretory multiple myeloma. *Blood,* **97,** 2900-2902.

Drayson, M., Begum, G., Basu, S., Makkuni, S., Dunn, J., Barth, N. & Child, J.A. (2006) Effects of paraprotein heavy and light chain types and free light chain load on survival in myeloma: an analysis of patients receiving conventional-dose chemotherapy in Medical Research Council UK multiple myeloma trials. *Blood,* **108,** 2013-2019.

Drayson, M.T., Behrens, J., Cohen, D.R., Iggo, N., Gregory, W.M., Bell, S.E., Howie, A., Samson, D., Jackson, G.H. & Gaskin, G. (2009) Serum FLC levels can be reduced rapidly ; lower levels are associated with renal recovery. *Clinical Lymphoma and Myeloma,* **9 Suppl 1,** Abstract 351.

Durie, B.G. (2006) The role of anatomic and functional staging in myeloma: description of Durie/Salmon plus staging system. *European Journal of Cancer,* **42,** 1539-1543.

Durie, B.G. & Salmon, S.E. (1975) A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. *Cancer,* **36,** 842-854.

Durie, B.G., Harousseau, J.L., Miguel, J.S., Blade, J., Barlogie, B., Anderson, K., Gertz, M., Dimopoulos, M., Westin, J., Sonneveld, P., Ludwig, H., Gahrton, G., Beksac, M., Crowley, J., Belch, A., Boccadaro, M., Cavo, M., Turesson, I., Joshua, D., Vesole, D., Kyle, R., Alexanian, R., Tricot, G., Attal, M., Merlini, G., Powles, R., Richardson, P., Shimizu, K., Tosi, P., Morgan, G. & Rajkumar, S.V. (2006) International uniform response criteria for multiple myeloma. *Leukemia,* **20,** 1467-1473.

Einsele, H., Liebisch, P., Langer, C., Kropff, M., Wandt, H., Jung, W., Kröger, N., Engelhardt, M., Ostermann, H., Mügge, L.-O., Wolf, H.-H., Hart, C., Metzner, B., Kaufmann, M., Gramatzki, M., Hertenstein, B., Fischer, T., Weisel, K., Dölken, G., Brugger, W., Gollasch, H., Maschmeyer, G., Pfreundschuh, M., Schmitz, N., Sezer, O., Heidemann, E., Jäger, E., Kahl, C., Kiani, A., Dechow, T., Rösler, W., Simon, J.P., Dürk, H., Pflüger, K.H., Bentz, M., Hess, G., Mergenthaler, H.-G., Straka, C., Hempel, D., Salwender, H.-J., Fingerle-Rowson, G. & Knop, S. (2009) Velcade, intravenous cyclophosphamide and dexamethasone (VCD) induction for previously untreated multiple myeloma (German DSMM XIa trial). *Blood (ASH Annual Meeting Abstracts),* **114,** Abstract 131.

Eleutherakis-Papaiakovou, V., Bamias, A., Gika, D., Simeonidis, A., Pouli, A., Anagnostopoulos, A., Michali, E., Economopoulos, T., Zervas, K. & Dimopoulos, M.A. (2007) Renal failure in multiple myeloma: incidence, correlations, and prognostic significance. *Leukemia and Lymphoma,* **48,** 337-341.

Endo, T., Okumura, H., Kikuchi, K., Munakata, J., Otake, M., Nomura, T. & Asakawa, H. (1981) Immunoglobulin E (IgE) multiple myeloma: a case report and review of the literature. *American Journal of Medicine,* **70,** 1127-1132.

Eriksson, T., Hoglund, P., Turesson, I., Waage, A., Don, B.R., Vu, J., Scheffler, M. & Kaysen, G.A. (2003) Pharmacokinetics of thalidomide in patients with impaired renal function and while on and off dialysis. *Journal of Pharmacy and Pharmacology,* **55,** 1701-1706.

Facon, T., Mary, J.Y., Hulin, C., Benboubker, L., Attal, M., Pegourie, B., Renaud, M., Harousseau, J.L., Guillerm, G., Chaleteix, C., Dib, M., Voillat, L., Maisonneuve, H., Troncy, J., Dorvaux, V., Monconduit, M., Martin, C., Casassus, P., Jaubert, J., Jardel, H., Doyen, C., Kolb, B., Anglaret, B., Grosbois, B., Yakoub-Agha, I., Mathiot, C. & Avet-Loiseau, H. (2007) Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. *Lancet,* **370,** 1209-1218.

Fermand, J.P., Ravaud, P., Chevret, S., Divine, M., Leblond, V., Belanger, C., Macro, M., Pertuiset, E., Dreyfus, F., Mariette, X., Boccacio, C. & Brouet, J.C. (1998) High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: up-front or rescue treatment? Results of a multicenter sequential randomized clinical trial. *Blood,* **92,** 3131-3136.

Feyler, S., Rawstron, A., Jackson, G., Snowden, J.A., Cocks, K. & Johnson, R.J. (2007) Thalidomide maintenance following high-dose therapy in multiple myeloma: a UK myeloma forum phase 2 study. *British Journal of Haematology,* **139,** 429-433.

Feyler, S., O'Connor, S.J., Rawstron, A.C., Subash, C., Ross, F.M., Pratt, G., Drayson, M.T., Ashcroft, J., Cook, G. & Owen, R.G. (2008) IgM myeloma: a rare entity characterized by a CD20-CD56-CD117- immunophenotype and the t(11;14). *British Journal of Haematology,* **140,** 547-551.

Fietz, T., Rieger, K., Dimeo, F., Blau, I.W., Thiel, E. & Knauf, W.U. (2004) Stem cell mobilization in multiple myeloma patients: do we need an age-adjusted regimen for the elderly? *Journal of Clinical Apheresis,* **19,** 202-207.

Finnegan, D.P., Kettle, P., Drake, M., Matthews, C., Alexander, H.D., Popat, R., Cavanagh, J.D., Wachsman, W. & Morris, T.C. (2006) Bortezomib is effective in primary plasma cell leukemia. *Leukemia and Lymphoma,* **47,** 1670-1673.

Fonseca, R., Van Wier, S.A., Chng, W.J., Ketterling, R., Lacy, M.Q., Dispenzieri, A., Bergsagel, P.L., Rajkumar, S.V., Greipp, P.R., Litzow, M.R., Price-Troska, T., Henderson, K.J., Ahmann, G.J. & Gertz, M.A. (2006) Prognostic value of chromosome 1q21 gain by fluorescent in situ hybridization and increase CKS1B expression in myeloma. *Leukemia,* **20,** 2034-2040.

Fonseca, R., Bergsagel, P.L., Drach, J., Shaughnessy, J., Gutierrez, N., Stewart, A.K., Morgan, G., Van Ness, B., Chesi, M., Minvielle, S., Neri, A., Barlogie, B., Kuehl, W.M., Liebisch, P., Davies, F., Chen-Kiang, S., Durie, B.G., Carrasco, R., Sezer, O., Reiman, T., Pilarski, L. & Avet-Loiseau, H. (2009) International Myeloma Working Group molecular classification of multiple myeloma: spotlight review. *Leukemia,* **23,** 2210-2221.

Fritz, E. & Ludwig, H. (2000) Interferon-alpha treatment in multiple myeloma: meta-analysis of 30 randomised trials among 3948 patients. *Annals of Oncology,* **11,** 1427-1436.

Gahrton, G., Tura, S., Ljungman, P., Belanger, C., Brandt, L., Cavo, M., Facon, T., Granena, A., Gore, M., Gratwohl, A., Löwenberg, B., Nikoskelainen, J., Reiffers, J.J., Samson, D., Verdonck, L. & Volin, L. for the European Group for Bone Marrow Transplantation (1991) Allogeneic bone marrow transplantation in multiple myeloma. European Group for Bone Marrow Transplantation. *New England Journal of Medicine,* **325,** 1267-1273.

Gahrton, G., Svensson, H., Cavo, M., Apperly, J., Bacigalupo, A., Bjorkstrand, B., Blade, J., Cornelissen, J., de Laurenzi, A., Facon, T., Ljungman, P., Michallet, M., Niederwieser, D., Powles, R., Reiffers, J., Russell, N.H., Samson, D., Schaefer, U.W., Schattenberg, A., Tura, S., Verdonck, L.F., Vernant, J.P., Willemze, R. & Volin, L. (2001) Progress in allogenic bone marrow and peripheral blood stem cell transplantation for multiple myeloma: a comparison between transplants performed 1983-93 and 1994-98 at European Group for Blood and Marrow Transplantation centres. *British Journal of Haematology,* **113,** 209-216.

Garban, F., Attal, M., Michallet, M., Hulin, C., Bourhis, J.H., Yakoub-Agha, I., Lamy, T., Marit, G., Maloisel, F., Berthou, C., Dib, M., Caillot, D., Deprijck, B., Ketterer, N., Harousseau, J.L., Sotto, J.J. & Moreau, P. (2006) Prospective comparison of autologous stem cell transplantation followed by dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04 trial) in high-risk de novo multiple myeloma. *Blood,* **107,** 3474-3480.

Garcia-Sanz, R., Orfao, A., Gonzalez, M., Tabernero, M.D., Blade, J., Moro, M.J., Fernandez-Calvo, J., Sanz, M.A., Perez-Simon, J.A., Rasillo, A. & Miguel, J.F. (1999) Primary plasma cell leukemia: clinical, immunophenotypic, DNA ploidy, and cytogenetic characteristics. *Blood,* **93,** 1032-1037.

Garcia-Sanz, R., Gonzalez-Porras, J.R., Hernandez, J.M., Polo-Zarzuela, M., Sureda, A., Barrenetxea, C., Palomera, L., Lopez, R., Grande-Garcia, C., Alegre, A., Vargas-Pabon, M., Gutierrez, O.N., Rodriguez, J.A. & San Miguel, J.F. (2004) The oral combination of thalidomide, cyclophosphamide and dexamethasone (ThaCyDex) is effective in relapsed/refractory multiple myeloma. *Leukemia,* **18,** 856-863.

Gay, F., Bringhen, S., Genuardi, M., Rossi, D., Ria, R., Romano, A., Ferrara, F., Di Renzo, N., Dominietto, A., Andriani, A., Rizzi, R., Vallone, R., Mele, G., Storti, S., Podda, L., Aitoro, G., Mettivier, V., Annibali, O., Rossini, F., Gentilini, P., Pavone, V., Giuliani, N., Rauco, A.M., Baraldi, A., Capaldi, A., Gherlinzoni, F., Gaidano, G., Boccadoro, M. & Palumbo, A. (2009) The weekly infusion of bortezomib reduces peripheral neuropathy. *Blood (ASH Annual Meeting Abstracts),* **114,** Abstract 3887.

Gerull, S., Goerner, M., Benner, A., Hegenbart, U., Klein, U., Schaefer, H., Goldschmidt, H. & Ho, A.D. (2005) Long-term outcome of nonmyeloablative allogeneic transplantation in patients with high-risk multiple myeloma. *Bone Marrow Transplantation,* **36,** 963-969.

Glasmacher, A., Hahn, C., Hoffmann, F., Naumann, R., Goldschmidt, H., von Lilienfeld-Toal, M., Orlopp, K., Schmidt-Wolf, I. & Gorschluter, M. (2006) A systematic review of

phase-II trials of thalidomide monotherapy in patients with relapsed or refractory multiple myeloma. *British Journal of Haematology,* **132,** 584-593.

Gore, M.E., Selby, P.J., Viner, C., Clark, P.I., Meldrum, M., Millar, B., Bell, J., Maitland, J.A., Milan, S., Judson, I.R., Tillyer, C., Selby, P.J. & McElwain, T.J.. (1989) Intensive treatment of multiple myeloma and criteria for complete remission. *Lancet,* **2,** 879-882.

Greipp, P.R., San Miguel, J., Durie, B.G., Crowley, J.J., Barlogie, B., Blade, J., Boccadoro, M., Child, J.A., Avet-Loiseau, H., Kyle, R.A., Lahuerta, J.J., Ludwig, H., Morgan, G., Powles, R., Shimizu, K., Shustik, C., Sonneveld, P., Tosi, P., Turesson, I. & Westin, J. (2005) International staging system for multiple myeloma. *Journal of Clinical Oncology,* **23,** 3412-3420.

Gulbrandsen, N., Waage, A., Gimsing, P., Turesson, I., Juliusson, G., Abildgaard, N., Bjørkstrand, B., Carlson, K., Dahl, I.M., Forsberg, K., Knudsen, L.M., Nielsen, J.L., Mellqvist, U.H., Nesthus, I., Strandberg, M., Wisløff, F. & Fayers, P. (2008) A randomised placebo controlled study with melphalan/prednisone vs melphalan/prednisone/thalidomide: quality of life and toxicity. *Haematologica,* **95 (S1),** Abstract 0209.

Harousseau, J.L., Moreau, P., Attal, M., Facon, T. & Avet-Loiseau, H. (2005) Stem-cell transplantation in multiple myeloma. *Best Practice & Research Clinical Haematology,* **18,** 603-618.

Harousseau, J.L., Attal, M., Leleu, X., Troncy, J., Pegourie, B., Stoppa, A.M., Hulin, C., Benboubker, L., Fuzibet, J.G., Renaud, M., Moreau, P. & Avet-Loiseau, H. (2006) Bortezomib plus dexamethasone as induction treatment prior to autologous stem cell transplantation in patients with newly diagnosed multiple myeloma: results of an IFM phase II study. *Haematologica,* **91,** 1498-1505.

Harousseau, J.L., Mathiot, C., Attal, M., Marit, G., Caillot, D., Hullin, C., Facon, T., Webb, I., Avet-Loiseau, H. & Moreau, P. (in press) Bortezomib/dexamethasone is superior to vincristine-doxorubicin-dexamethasone as induction treatment prior to autologous stem cell transplantion in newly diagnosed multiple myeloma: results of the IFM 2005/01 phase 3 trial. *Journal of Clinical Oncology*

Haslett, P.A., Hanekom, W.A., Muller, G. & Kaplan, G. (2003) Thalidomide and a thalidomide analogue drug costimulate virus-specific CD8+ T cells in vitro. *The Journal of Infectious Diseases,* **187,** 946-955.

Haubitz, M. & Peest, D. (2006) Myeloma--new approaches to combined nephrological-haematological management. *Nephrology Dialysis Transplantation,* **21,** 582-590.

Hicks, L.K., Haynes, A.E., Reece, D.E., Walker, I.R., Herst, J.A., Meyer, R.M. & Imrie, K. (2008) A meta-analysis and systematic review of thalidomide for patients with previously untreated multiple myeloma. *Cancer Treatment Reviews,* **34,** 442-452.

Hideshima, T., Chauhan, D., Shima, Y., Raje, N., Davies, F.E., Tai, Y.T., Treon, S.P., Lin, B., Schlossman, R.L., Richardson, P., Muller, G., Stirling, D.I. & Anderson, K.C. (2000) Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy. *Blood,* **96,** 2943-2950.

Hideshima, T., Richardson, P., Chauhan, D., Palombella, V.J., Elliott, P.J., Adams, J. & Anderson, K.C. (2001) The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells. *Cancer Research,* **61,** 3071-3076.

Hjorth, M., Hellquist, L., Holmberg, E., Magnusson, B., Rodjer, S. & Westin, J. (1993) Initial versus deferred melphalan-prednisone therapy for asymptomatic multiple myeloma stage I--a randomized study. Myeloma Group of Western Sweden. *European Journal of Haematology,* **50,** 95-102.

Hughes, M., Soutar, R., Lucraft, H., Owen, R. & Bird, J. (2009) Guidelines on the diagnosis and management of solitary plasmacytoma of bone, extramedullary plasmacytoma and multiple

solitary plasmacytomas: 2009 update
http://www.bcshguidelines.com/pdf/SBP_guideline_update_FINAL_190109.pdf.
Hulin, C., Facon, T., Rodon, P., Pegourie, B., Benboubker, L., Doyen, C., Dib, M., Guillerm, G., Salles, B., Eschard, J.P., Lenain, P., Casassus, P., Azaïs, I., Decaux, O., Garderet, L., Mathiot, C., Fontan, J., Lafon, I., Virion, J.M., Moreau, P. (2009) Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial. *Journal of Clinical Oncology*. **27**: 3664-70.
Hunter, H.M., Peggs, K., Powles, R., Rahemtulla, A., Mahendra, P., Cavenagh, J., Littlewood, T., Potter, M., Hunter, A., Pagliuca, A., Williams, C.D., Cook, G., Towlson, K., Marks, D.I. & Russell, N.H. (2005) Analysis of outcome following allogeneic haemopoietic stem cell transplantation for myeloma using myeloablative conditioning--evidence for a superior outcome using melphalan combined with total body irradiation. *British Journal of Haematology,* **128,** 496-502.
Hutchison, C.A., Plant, T., Drayson, M., Cockwell, P., Kountouri, M., Basnayake, K., Harding, S., Bradwell, A.R. & Mead, G. (2008) Serum free light chain measurement aids the diagnosis of myeloma in patients with severe renal failure. *BMC Nephrology,* **22,** 9-11.
Iggo, N., Winearls, C.G. & Davies, D.R. (1997) The development of cast nephropathy in multiple myeloma. *Quarterly Journal of Medicine,* **90,** 653-656.
International Myeloma Working Group (2003) Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the. *British Journal of Haematology,* **121,** 749-757.

Jagannath, S., Barlogie, B., Berenson, J.R., Singhal, S., Alexanian, R., Srkalovic, G., Orlowski, R.Z., Richardson, P.G., Anderson, J., Nix, D., Esseltine, D.L. & Anderson, K.C. (2005a) Bortezomib in recurrent and/or refractory multiple myeloma. Initial clinical experience in patients with impared renal function. *Cancer,* **103,** 1195-1200.
Jagannath, S., Durie, B.G., Wolf, J., Camacho, E., Irwin, D., Lutzky, J., McKinley, M., Gabayan, E., Mazumder, A., Schenkein, D. & Crowley, J. (2005b) Bortezomib therapy alone and in combination with dexamethasone for previously untreated symptomatic multiple myeloma. *British Journal of Haematology,* **129,** 776-783.
Jakubowiak, A.J., Al-Zoubi, A., Kendall, T., Friedman, J., Ahmed, A., Khaled, Y., Mineishi, S. & Kaminski, M.S. (2006) High rate of complete and near complete responses (CR/nCR) after initial therapy with bortezomib (velcade®), doxil®, and dexamethasone (VDD) is further increased after autologous stem cell transplantation (ASCT). *Blood (ASH Annual Meeting Abstracts),* **108,** Abstract 3093.
Jancelewicz, Z., Takatsuki, K., Sugai, S. & Pruzanski, W. (1975) IgD multiple myeloma. Review of 133 cases. *Archives of Internal Medicine,* **135,** 87-93.
Jantunen, E. (2006) Autologous stem cell transplantation beyond 60 years of age. *Bone Marrow Transplantation,* **38,** 715-720.
Johnson, W.J., Kyle, R.A., Pineda, A.A., O'Brien, P.C. & Holley, K.E. (1990) Treatment of renal failure associated with multiple myeloma. Plasmapheresis, hemodialysis, and chemotherapy. *Archives of Internal Medicine,* **150,** 863-869.
Kairemo, K.J., Lindberg, M. & Prytz, M. (1999) IgE myeloma: a case presentation and a review of the literature. *Scandinavian Journal of Clinical and Laboratory Investigation,* **59,** 451-456.
Kapoor, P., Kumar, S., Fonseca, R., Lacy, M.Q., Witzig, T.E., Hayman, S.R., Dispenzieri, A., Buadi, F., Bergsagel, P.L., Gertz, M.A., Dalton, R.J., Mikhael, J.R., Dingli, D., Reeder, C.B., Lust, J.A., Russell, S.J., Roy, V., Zeldenrust, S.R., Stewart, A.K., Kyle, R.A., Greipp, P.R. & Rajkumar, S.V. (2009) Impact of risk stratification on outcome among patients with multiple myeloma receiving initial therapy with lenalidomide and dexamethasone. *Blood,* **114,** 518-521.
Kastritis, E., Anagnostopoulos, A., Roussou, M., Gika, D., Matsouka, C., Barmparousi, D., Grapsa, I., Psimenou, E., Bamias, A. & Dimopoulos, M.A. (2007) Reversibility of renal

failure in newly diagnosed multiple myeloma patients treated with high dose dexamethasone-containing regimens and the impact of novel agents. *Haematologica,* **92,** 546-549.

Knudsen, L.M., Hippe, E., Hjorth, M., Holmberg, E. & Westin, J. (1994) Renal function in newly diagnosed multiple myeloma--a demographic study of 1353 patients. The Nordic Myeloma Study Group. *European Journal of Haematology,* **53,** 207-212.

Knudsen, L.M., Hjorth, M. & Hippe, E. (2000) Renal failure in multiple myeloma: reversibility and impact on the prognosis. Nordic Myeloma Study Group. *European Journal of Haematology,* **65,** 175-181.

Knudsen, L.M., Nielsen, B., Gimsing, P. & Geisler, C. (2005) Autologous stem cell transplantation in multiple myeloma: outcome in patients with renal failure. *European Journal of Haematology,* **75,** 27-33.

Konduri, K., Sahota, S.S., Babbage, G., Tong, A.W., Kumar, P., Newman, J.T. & Stone, M.J. (2005) Immunoglobulin M myeloma: evaluation of molecular features and cytokine expression. *Clinical Lymphoma,* **5**, 285-289.

Kröger, N., Sayer, H.G., Schwerdtfeger, R., Kiehl, M., Nagler, A., Renges, H., Zabelina, T., Fehse, B., Ayuk, F., Wittkowsky, G., Schmitz, N. & Zander, A.R. (2002) Unrelated stem cell transplantation in multiple myeloma after a reduced-intensity conditioning with pretransplantation antithymocyte globulin is highly effective with low transplantation-related mortality. *Blood,* **100,** 3919-3924.

Kröger, N., Einsele, H., Wolff, D., Casper, J., Freund, M., Derigs, G., Wandt, H., Schäfer-Eckart, K., Wittkowsky, G., Schmitz, N., Krüger, W., Zabelina, T., Renges, H., Ayuk, F., Krüll, A., Zander, A.; German Study- group Multiple Myeloma (DSMM). (2003) Myeloablative intensified conditioning regimen with in vivo T-cell depletion (ATG) followed by allografting in patients with advanced multiple myeloma. A phase I/II study of the German Study-group Multiple Myeloma (DSMM). *Bone Marrow Transplantation* **31**, 973-9.

Kröger, N., Shimoni, A., Zagrivnaja, M., Ayuk, F., Lioznov, M., Schieder, H., Renges, H., Fehse, B., Zabelina, T., Nagler, A. & Zander, A.R. (2004) Low-dose thalidomide and donor lymphocyte infusion as adoptive immunotherapy after allogeneic stem cell transplantation in patients with multiple myeloma. *Blood,* **104,** 3361-3363.

Kropff, M.H., Lang, N., Bisping, G., Domine, N., Innig, G., Hentrich, M., Mitterer, M., Sudhoff, T., Fenk, R., Straka, C., Heinecke, A., Koch, O.M., Ostermann, H., Berdel, W.E. & Kienast, J. (2003) Hyperfractionated cyclophosphamide in combination with pulsed dexamethasone and thalidomide (HyperCDT) in primary refractory or relapsed multiple myeloma. *British Journal of Haematology,* **122,** 607-616.

Kumar, S., Lacy, M.Q., Dispenzieri, A., Rajkumar, S.V., Fonseca, R., Geyer, S., Allmer, C., Witzig, T.E., Lust, J.A., Greipp, P.R., Kyle, R.A., Litzow, M.R. & Gertz, M.A. (2004) High-dose therapy and autologous stem cell transplantation for multiple myeloma poorly responsive to initial therapy. *Bone Marrow Transplantation,* **34,** 161-167.

Kumar, S., Dispenzieri, A., Lacy, M.Q., Hayman, S.R., Buadi, F.K., Gastineau, D.A., Litzow, M.R., Fonseca, R., Roy, V., Rajkumar, S.V. & Gertz, M.A. (2007) Impact of lenalidomide therapy on stem cell mobilization and engraftment post-peripheral blood stem cell transplantation in patients with newly diagnosed myeloma. *Leukemia,* **21,** 2035-2042.

Kumar, S.K., Rajkumar, S.V., Dispenzieri, A., Lacy, M.Q., Hayman, S.R., Buadi, F.K., Zeldenrust, S.R., Dingli, D., Russell, S.J., Lust, J.A., Greipp, P.R., Kyle, R.A. & Gertz, M.A. (2008a) Improved survival in multiple myeloma and the impact of novel therapies. *Blood,* 111, 2516-2520.

Kumar, S.K., Dingli, D., Lacy, M.Q., Dispenzieri, A., Hayman, S.R., Buadi, F.K., Rajkumar, S.V., Litzow, M.R. & Gertz, M.A. (2008b) Autologous stem cell transplantation in patients of 70 years and older with multiple myeloma: Results from a matched pair analysis. *American Journal of Hematology,* 83, 614-617.

Kumar, S., Hayman, S., Buadi, F., Lacy, M., Stewart, K., Allred, J., Lauman, K., McCarty, T., Bergsagel, L., Dingli, D., Fonseca, R., Gertz, M., Greipp, P., Lust, J., Russell, S., Reeder, C., Witzig, T., Zeldenrust, S., Kyle, R., Rajkumar, S.V. & Dispenzieri, A. (2008c) Phase II trial of lenalidomide (revlimidTM) with cyclophosphamide and dexamethasone (RCd) for newly diagnosed myeloma. *Blood (ASH Annual Meeting Abstracts),* **112,** Abstract 91.

Kumar, A., Kharfan-Dabaja, M.A., Glasmacher, A. & Djulbegovic, B. (2009a) Tandem versus single autologous hematopoietic cell transplantation for the treatment of multiple myeloma: a systematic review and meta-analysis. *Journal of the National Cancer Institute,* **101,** 100-106.

Kumar, S., Flinn, I.W., Parameswaran, Hari, N., Callander, N., Noga, S.J., Stewart, A.K., Glass, J., Raje, N., Rifkin, R.M., Shi, H., Webb, I.J., Richardson, P.G. & Rajkumar, S.V. (2009b) Novel three- and four-drug combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide, for newly diagnosed multiple myeloma: encouraging results from the multi-center, randomized, phase 2 EVOLUTION Study. *Blood (ASH Annual Meeting Abstracts),* **114,** Abstract 127.

Kuruvilla J, Shepherd JD, Sutherland HJ, Nevill TJ, Nitta J, Le A, Forrest DL, Hogge DE, Lavoie JC, Nantel SH, Toze CL, Smith CA, Barnett MJ, Song KW (2007). Long-term outcome of myeloablative allogeneic stem cell transplantation for multiple myeloma. *Biology of Blood and Marrow Transplantation*, **13**, 925-31.

Kyle, R.A. (1975) Multiple myeloma: review of 869 cases. *Mayo Clinic Proceedings,* **50,** 29-40.

Kyle, R.A., Maldonado, J.E. & Bayrd, E.D. (1974) Plasma cell leukemia. Report on 17 cases. *Archives of Internal Medicine,* **133,** 813-818.

Kyle, R.A., Gertz, M.A., Witzig, T.E., Lust, J.A., Lacy, M.Q., Dispenzieri, A., Fonseca, R., Rajkumar, S.V., Offord, J.R., Larson, D.R., Plevak, M.E., Therneau, T.M. & Greipp, P.R. (2003) Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clinic Proceedings,* **78,** 21-33.

Kyle, R.A., Remstein, E.D., Therneau, T.M., Dispenzieri, A., Kurtin, P.J., Hodnefield, J.M., Larson, D.R., Plevak, M.F., Jelinek, D.F., Fonseca, R., Melton, L.J., 3rd & Rajkumar, S.V. (2007) Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. *New England Journal of Medicine,* **356,** 2582-2590.

Kyriakou, C., Thomson, K., D'Sa, S., Flory, A., Hanslip, J., Goldstone, A.H. & Yong, K.L. (2005) Low-dose thalidomide in combination with oral weekly cyclophosphamide and pulsed dexamethasone is a well tolerated and effective regimen in patients with relapsed and refractory multiple myeloma. *British Journal of Haematology,* **129,** 763-770.

Lacy, M.Q., Hayman, S.R., Gertz, M.A., Dispenzieri, A., Buadi, F., Kumar, S., Greipp, P.R., Lust, J.A., Russell, S.J., Dingli, D., Kyle, R.A., Fonseca, R., Bergsagel, P.L., Roy, V., Mikhael, J.R., Stewart, A.K., Laumann, K., Allred, J.B., Mandrekar, S.J., Rajkumar, S.V. (2009) Pomalidomide (CC4047) plus low-dose dexamethasone as therapy for relapsed multiple myeloma. *Journal of Clinical Oncology*, 27(30):5008-14.

Lahtinen, R., Laakso, M., Palva, I., Virkkunen, P. & Elomaa, I. (1992) Randomised, placebo-controlled multicentre trial of clodronate in multiple myeloma. Finnish Leukaemia Group. *Lancet,* **340,** 1049-1052.

Lahuerta, J.J., Mateos, M.V., Martínez-López, J., Rosiñol, L., Sureda, A., de la Rubia, J., García-Laraña, J., Martínez-Martínez, R., Hernández-García, M.T., Carrera, D., Besalduch, J., de Arriba, F., Ribera, J.M., Escoda, L., Hernández-Ruiz, B., García-Frade, J., Rivas-González, C., Alegre, A., Bladé, J. & San Miguel, J.F. (2008) Influence of pre- and post-transplantation responses on outcome of patients with multiple myeloma: sequential improvement of response and achievement of complete response are associated with longer survival. *Journal of Clinical Oncology,* **26,** 5775-5782.

Landgren, O., Kyle, R.A., Pfeiffer, R.M., Katzmann, J.A., Caporaso, N.E., Hayes, R.B., Dispenzieri, A., Kumar, S., Clark, R.J., Baris, D., Hoover, R. & Rajkumar, S.V. (2009)

Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. Blood, 113, 5412-5417.

Le Blanc, R., Montminy-Metivier, S., Belanger, R., Busque, L., Fish, D., Roy, D.C., Kassis, J., Boileau, J., Lavallee, R., Belanger, D., Letendre, F., Hebert, J., Sauvageau, G., Perreault, C. & Roy, J. (2001) Allogeneic transplantation for multiple myeloma: further evidence for a GVHD-associated graft-versus-myeloma effect. *Bone Marrow Transplantation*, 28, 841-848.

Lee CK, Barlogie B, Munshi N, Zangari M, Fassas S, Jacobson J, van Rhee F, Cottler-Fox M, Muwalla F, Tricot G (2003a) DTPACE : an effective, novel combination chemotherapy with thalidomide for previously treated patients with myeloma. J Clin Oncol; 21:2732-9.

Lee, C.K., Badros, A., Barlogie, B., Morris, C., Zangari, M., Fassas, A., van Rhee, F., Cottler-Fox, M., Jacobson, J., Thertulien, R., Muwalla, F., Mazher, S., Anaissie, E., Tricot, G.. (2003b) Prognostic factors in allogeneic transplantation for patients with high-risk multiple myeloma after reduced intensity conditioning. *Experimental Hematology*. 31, 73-80.

Lee, C.K., Zangari, M., Barlogie, B., Fassas, A., van Rhee, F., Thertulien, R., Talamo, G., Muwalla, F., Anaissie, E., Hollmig, K. & Tricot, G. (2004) Dialysis-dependent renal failure in patients with myeloma can be reversed by high-dose myeloablative therapy and autotransplant. *Bone Marrow Transplantation,* **33,** 823-828.

Lokhorst, H.M., Segeren, C.M., Verdonck, L.F., van der Holt, B., Raymakers, R., van Oers, M.H., Barge, R.M., Schouten, H.C., Westveer, P.H., Steijaert, M.M., Cornelissen, J.J. & Sonneveld, P. (2003) Partially T-cell-depleted allogeneic stem-cell transplantation for first-line treatment of multiple myeloma: a prospective evaluation of patients treated in the phase III study HOVON 24 MM. *Journal of Clinical Oncology,* **21,** 1728-1733.

Lokhorst, H.M., Wu, K., Verdonck, L.F., Laterveer, L.L., van de Donk, N.W., van Oers, M.H., Cornelissen, J.J. & Schattenberg, A.V. (2004) The occurrence of graft-versus-host disease is the major predictive factor for response to donor lymphocyte infusions in multiple myeloma. *Blood,* **103,** 4362-4364.

Lokhorst, H., Sonneveld, P. & Van der Holt, B. (2008) Donor versus no donor analysis of newly diagnosed myeloma patients included in the HOVON 50/54 study. *Blood (ASH Annual Meeting Abstracts),* **112,** 461.

Lokhorst, H.M., van der Holt, B., Zweegman, S., Vellenga, E., Croockewit, S., van Oers, M.H., von dem Borne, P., Wijermans, P., Schaafsma, R., de Weerdt, O., Wittebol, S., Delforge, M., Berenschot, H., Bos, G.M., Jie, K.S., Sinnige, H., van Marwijk-Kooy, M., Joosten, P., Minnema, M.C., van Ammerlaan, R. & Sonneveld, P. (2010) Dutch-Belgian Hemato-Oncology Group (HOVON). A randomized phase 3 study on the effect of thalidomide combined with adriamycin, dexamethasone, and high-dose melphalan, followed by thalidomide maintenance in patients with multiple myeloma. *Blood,* **115,** 1113-1120.

Lonial, S. & Cavenagh, J. (2009) Emerging combination treatment strategies containing novel agents in newly diagnosed multiple myeloma. *British Journal of Haematology,* **145,** 681-708.

Ludwig, H., Hajek, R., Tóthová, E., Drach, J., Adam, Z., Labar, B., Egyed, M., Spicka, I., Gisslinger, H., Greil, R., Kuhn, I., Zojer, N. & Hinke, A. (2009a) Thalidomide-dexamethasone compared with melphalan-prednisolone in elderly patients with multiple myeloma. *Blood,* **113,** 3435-3442.

Ludwig H., Adam Z., Greil R., Tthov E., Keil F., Zojer N., Thaler J., Gisslinger H., Egyed M., Lang A. (2009b) Reversal of acute renal impairment by bortezomib-doxorubicin-dexamethasone (BDD) in multiple myeloma. Results from a Phase II study. *Haematologica.* **94,** 154 (abstract 0385).

Macro, M., Divine, M., Uzunhan, Y., Jaccard, A., Bouscary, D., Leblond, V., Janvier, M., Genet, P., Castaigne, S., Royer, B., Allard, C., Chevret, S. & Fermand, J.-P. (2006) Dexamethasone+thalidomide (Dex/Thal) compared to VAD as a pre-transplant treatment in newly diagnosed multiple myeloma (MM): A randomized trial. *Blood (ASH Annual Meeting Abstracts),* **108,** Abstract 57.

Major, P., Lortholary, A., Hon, J., Abdi, E., Mills, G., Menssen, H.D., Yunus, F., Bell, R., Body, J., Quebe-Fehling, E. & Seaman, J. (2001) Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *Journal of Clinical Oncology,* **19,** 558-567.

Maloney, D.G., Molina, A.J., Sahebi, F., Stockerl-Goldstein, K.E., Sandmaier, B.M., Bensinger, W., Storer, B., Hegenbart, U., Somlo, G., Chauncey, T., Bruno, B., Appelbaum, F.R., Blume, K.G., Forman, S.J., McSweeney, P. & Storb, R. (2003) Allografting with nonmyeloablative conditioning following cytoreductive autografts for the treatment of patients with multiple myeloma. *Blood,* **102,** 3447-3454.

Mark, T., Stern, J., Furst, J.R., Jayabalan, D., Zafar, F., LaRow, A., Pearse, R.N., Harpel, J., Shore, T., Schuster, M.W., Leonard, J.P., Christos, P.J., Coleman, M. & Niesvizky, R. (2008) Stem cell mobilization with cyclophosphamide overcomes the suppressive effect of lenalidomide therapy on stem cell collection in multiple myeloma. *Biology of Blood and Marrow Transplantation,* **14,** 795-798.

Mateos, M.V., Hernández, J.M., Hernández, M.T., Gutiérrez, N.C., Palomera, L., Fuertes, M., Garcia-Sanchez, P., Lahuerta, J.J., de la Rubia, J., Terol, M.J., Sureda, A., Bargay, J., Ribas, P., Alegre, A., de Arriba, F., Oriol, A., Carrera, D., García-Laraña, J., García-Sanz, R., Bladé, J., Prósper, F., Mateo, G., Esseltine, D.L., van de Velde, H. & San Miguel, J.F. (2008) Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: updated time-to-events results and prognostic factors for time to progression. *Haematologica,* **93,** 560-565.

Mateos, M.V., Oriol, A., Martínez-López, J., Gutiérrez, N., Teruel, A., de Paz, R., García-Laraña, J., Bengoechea, E., Martín, A., Mediavilla, J.D., Palomera, L., de Arriba, F., González, Y., Hernández, J.M., Sureda, A., Bello, J.L., Bargay, J., Peñalver, F.J., Ribera, J.M., Martín-Mateos, M.L., García-Sanz, R., Cibeira, M.T., Ramos, M.L., Vidriales, M.B., Paiva, B., Montalbán, M.A., Lahuerta, J.J., Bladé, J. & Miguel, J.F. (2010) Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial. *Lancet Oncology,* **11**: 934-41.

McCarthy, P.L., Owzar, K., Anderson, K.C., Hofmeister, C.C., Hassoun, H., Hurd, D.D., Stadtmauer, E.A., Giralt, S., Hars, V. & Linker, C.A. (2010) Phase III intergroup study of lenalidomide versus placebo maintenance therapy following single autologous stem cell transplant (ASCT) for multiple myeloma (MM): CALGB 100104. *Journal of Clinical Oncology,* **28,** 15s (abstract 8017).

McCloskey, E.V., MacLennan, I.C., Drayson, M.T., Chapman, C., Dunn, J. & Kanis, J.A. (1998) A randomized trial of the effect of clodronate on skeletal morbidity in multiple myeloma. MRC Working Party on Leukaemia in Adults. *British Journal of Haematology,* **100,** 317-325.

McCloskey, E.V., Dunn, J.A., Kanis, J.A., MacLennan, I.C. & Drayson, M.T. (2001) Long-term follow-up of a prospective, double-blind, placebo-controlled randomized trial of clodronate in multiple myeloma. *British Journal of Haematology,* **113,** 1035-1043.

McElwain, T.J. & Powles, R.L. (1983) High-dose intravenous melphalan for plasma-cell leukaemia and myeloma. *Lancet,* **2,** 822-824.

Mead, G.P. & Drayson, M.T. (2009) Sensitivity of serum free light chain measurement of residual disease in multiple myeloma patients. *Blood,* **114,** 1717.

Mead, G.P., Carr-Smith, H.D., Drayson, M.T., Morgan, G.J., Child, J.A. & Bradwell, A.R. (2004) Serum free light chains for monitoring multiple myeloma. *British Journal of Haematology,* **126,** 348-54.

Mehta, J. & Singhal, S. (2003) Hyperviscosity syndrome in plasma cell dyscrasias. *Seminars in Thrombosis and Hemostasis,* **29,** 467-471.

Menssen, H.D., Sakalova, A., Fontana, A., Herrmann, Z., Boewer, C., Facon, T., Lichinitser, M.R., Singer, C.R., Euller-Ziegler, L., Wetterwald, M., Fiere, D., Hrubisko, M., Thiel, E. & Delmas, P.D. (2002) Effects of long-term intravenous ibandronate therapy on skeletal-related events, survival, and bone resorption markers in patients with advanced multiple myeloma. *Journal of Clinical Oncology,* **20,** 2353-2359.

Mikhael, J.R., Samiee, S., Stewart, A.K., Chen, C., Trudel, S., Franke, N., Winter, A., Chang, H. & Reece, D.E. (2004) Outcome after second autologous stem cell transplantation as salvage therapy in patients with relapsed multiple myeloma. *Blood (ASH Annual Meeting Abstracts),* **104,** Abstract 943.

Mohty, B., El-Cheikh, J., Yakoub-Agha, I., Moreau, P., Harousseau, J.L. & Mohty, M. (2010) Peripheral neuropathy and new treatments for multiple myeloma: background and practical recommendations. *Haematologica,* **95,** 311-319.

Mohty, M., Boiron, J.M., Damaj, G., Michallet, A.S., Bay, J.O., Faucher, C., Perreau, V., Bilger, K., Coso, D., Stoppa, A.M., Tabrizi, R., Gastaut, J.A., Michallet, M., Maraninchi, D. & Blaise, D. (2004) Graft-versus-myeloma effect following antithymocyte globulin-based reduced intensity conditioning allogeneic stem cell transplantation. *Bone Marrow Transplantation,* **34,** 77-84.

Moreau, P., Facon, T., Attal, M., Hulin, C., Michallet, M., Maloisel, F., Sotto, J.J., Guilhot, F., Marit, G., Doyen, C., Jaubert, J., Fuzibet, J.G., Francois, S., Benboubker, L., Monconduit, M., Voillat, L., Macro, M., Berthou, C., Dorvaux, V., Pignon, B., Rio, B., Matthes, T., Casassus, P., Caillot, D., Najman, N., Grosbois, B., Bataille, R. & Harousseau, J.L. (2002) Comparison of 200 mg/m(2) melphalan and 8 Gy total body irradiation plus 140 mg/m(2) melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myelome 9502 randomized trial. *Blood,* **99,** 731-735.

Morgan, G.I., Davies, F.E., Gregory, W.M., Bell, S.E., Szubert, A.J., Cocks, K., Navarro Coy, N., Drayson, M.T., Owen, R.G., Ross, F.M., Jackson, G.H. & Child, J.A. (2009) The addition of thalidomide to the induction treatment of newly presenting myeloma patients increases the CR rate which is likely to translate into improved PFS and OS. *Blood (ASH Annual Meeting Abstracts),* **114,** 352.

Morgan G., Davies F., Gregory W., Bell S.E., Szubert A., Navarro Coy N., Drayson M., Owen R.G., Jackson G.H., Child J.A. (2010) Evaluating the effects of zoledronic acid (ZOL) on overall survival (OS) in patients (Pts) with multiple myeloma (MM): Results of the Medical Research Council (MRC) Myeloma IX study J Clin Oncol 28:7s, (suppl; abstr 8021)

Morris, C., Iacobelli, S., Brand, R., Bjorkstrand, B., Drake, M., Niederwieser, D. & Gahrton, G. (2004) Benefit and timing of second transplantations in multiple myeloma: clinical findings and methodological limitations in a European Group for Blood and Marrow Transplantation registry study. *Journal of Clinical Oncology,* **22,** 1674-1681.

Morris, C.L., Siegel, E., Barlogie, B., Cottler-Fox, M., Lin, P., Fassas, A., Zangari, M., Anaissie, E. & Tricot, G. (2003) Mobilization of CD34+ cells in elderly patients (>/= 70 years) with multiple myeloma: influence of age, prior therapy, platelet count and mobilization regimen. *British Journal of Haematology,* **120,** 413-423.

Morris, *C.*, Drake, *M.*, Apperley, *J.*, Iacobelli, *S.*, van Biezen, S., Bjorkstrand, *B.*, Goldschmidt,*H.*, Jouet, J.P., Harousseau, *J-L*, Morgan, *G.*, de Witte, *T.*, Niederwieser, *D.*, Gahrton, *G.* for the myeloma subcommittee of the chronic leukaemia working party of the EBMT

(2010) Efficacy and outcome of autologous transplantation in rare myelomas. *Haematologica, in press*

MRC Working Party for Therapeutic Trials in Leukaemia (1971) Myelomatosis: comparison of melphalan and cyclophosphamide therapy. *British Medical Journal,* 1, 640-641.

MRC working party on leukaemia in adults (1984) Analysis and management of renal failure in fourth MRC myelomatosis trial.. *British Medical Journal,* **288,** 1411-1416.

Mulligan, G., Mitsiades, C., Bryant, B., Zhan, F., Chng, W.J., Roels, S., Koenig, E., Fergus, A., Huang, Y., Richardson, P., Trepicchio, W.L., Broyl, A., Sonneveld, P., Shaughnessy, J.D., Jr., Bergsagel, P.L., Schenkein, D., Esseltine, D.L., Boral, A. & Anderson, K.C. (2007) Gene expression profiling and correlation with outcome in clinical trials of the proteasome inhibitor bortezomib. *Blood,* **109,** 3177-3188.

Munshi, N.C., Avet-Loiseau, H. & Anderson, K.C. (2009) Guidelines for Risk Stratification in Multiple Myeloma . Report of the 2009 International Myeloma Workshop Consensus Panel 2. http://www.mw-delhi09.com/spargoDocs/Consensuspaneltwo.pdf.

Musto, P., Falcone, A., Sanpaolo, G., Bodenizza, C., Cascavilla, N., Melillo, L., Scalzulli, P.R., Dell'Olio, M., La Sala, A., Mantuano, S., Nobile, M. & Carella, A.M. (2003) Pamidronate reduces skeletal events but does not improve progression-free survival in early-stage untreated myeloma: results of a randomized trial. *Leukemia and Lymphoma,* **44,** 1545-1548.

Musto, P., Petrucci, M.T., Bringhen, S., Guglielmelli, T., Caravita, T., Bongarzoni, V., Andriani, A., D'Arena, G., Balleari, E., Pietrantuono, G., Boccadoro, M. & Palumbo, A. (2008) A multicenter, randomized clinical trial comparing zoledronic acid versus observation in patients with asymptomatic myeloma. *Cancer,* **113,** 1588-1595.

Myeloma Trialists' Collaborative Group. (1998) Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: an overview of 6,633 patients from 27 randomized trials. *Journal of Clinical Oncology,* **16,** 3832-3842.

National Institute for Health and Clinical Excellence. (2003) Improving outcomes in haematological cancers-The Manual. http://www.nice.org.uk/docref.asp?d=90429.

Ng, A.P., Wei, A., Bhurani, D., Chapple, P., Feleppa, F. & Juneja, S. (2006) The sensitivity of CD138 immunostaining of bone marrow trephine specimens for quantifying marrow involvement in MGUS and myeloma, including samples with a low percentage of plasma cells. *Haematologica,* **91,** 972-975.

Niesvizky, R., Jayabalan, D.S., Christos, P.J., Furst, J.R., Naib, T., Ely, S., Jalbrzikowski, J., Pearse, R.N., Zafar, F., Pekle, K., Larow, A., Lent, R., Mark, T., Cho, H.J., Shore, T., Tepler, J., Harpel, J., Schuster, M.W., Mathew, S., Leonard, J.P., Mazumdar, M., Chen-Kiang, S. & Coleman, M. (2008) BiRD (Biaxin [clarithromycin]/Revlimid [lenalidomide]/dexamethasone) combination therapy results in high complete- and overall-response rates in treatment-naive symptomatic multiple myeloma. *Blood,* **111,** 1101-1109.

Oakervee, H.E., Popat, R., Curry, N., Smith, P., Morris, C., Drake, M., Agrawal, S., Stec, J., Schenkein, D., Esseltine, D.L. & Cavenagh, J.D. (2005) PAD combination therapy (PS-341/bortezomib, doxorubicin and dexamethasone) for previously untreated patients with multiple myeloma. *British Journal of Haematology,* 129, 755-762.

O'Connor, O.A., Stewart, A.K., Vallone, M., Molineaux, C.J., Kunkel, L.A., Gerecitano, J.F., Orlowski, R.Z. (2009)A phase 1 dose escalation study of the safety and pharmacokinetics of the novel proteasome inhibitor carfilzomib (PR-171) in patients with hematologic malignancies. *Clinical Cancer Research*,**15:** 7085-91.

Orlowski, R.Z., Nagler, A., Sonneveld, P., Bladé, J., Hajek, R., Spencer, A., San Miguel, J., Robak, T., Dmoszynska, A., Horvath, N., Spicka, I., Sutherland, H.J., Suvorov, A.N., Zhuang, S.H., Parekh, T., Xiu, L., Yuan, Z., Rackoff, W. & Harousseau, J.L. (2007) Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma:

combination therapy improves time to progression. *Journal of Clinical Oncology,* **25,** 3892-3901.

Osterborg, A., Ehrsson, H., Eksborg, S., Wallin, I. & Mellstedt, H. (1989) Pharmacokinetics of oral melphalan in relation to renal function in multiple myeloma patients. *European Journal of Cancer & Clinical Oncology,* **25,** 899-903.

Paiva, B., Vidriales, M.B., Cervero, J., Mateo, G., Perez, J.J., Montalban, M.A., Sureda, A., Montejano, L., Gutierrez, N.C., Garcia de Coca, A., de Las Heras, N., Mateos, M.V., Lopez-Berges, M.C., Garcia-Boyero, R., Galende, J., Hernandez, J., Palomera, L., Carrera, D., Martinez, R., de la Rubia, J., Martin, A., Blade, J., Lahuerta, J.J., Orfao, A. & San Miguel, J.F. (2008) Multiparameter flow cytometric remission is the most relevant prognostic factor for multiple myeloma patients who undergo autologous stem cell transplantation. *Blood,* **112,** 4017-4023.

Palumbo, A., Giaccone, L., Bertola, A., Pregno, P., Bringhen, S., Rus, C., Triolo, S., Gallo, E., Pileri, A. & Boccadoro, M. (2001) Low-dose thalidomide plus dexamethasone is an effective salvage therapy for advanced myeloma. *Haematologica,* **86,** 399-403.

Palumbo, A., Bringhen, S., Petrucci, M.T., Musto, P., Rossini, F., Nunzi, M., Lauta, V.M., Bergonzi, C., Barbui, A., Caravita, T., Capaldi, A., Pregno, P., Guglielmelli, T., Grasso, M., Callea, V., Bertola, A., Cavallo, F., Falco, P., Rus, C., Massaia, M., Mandelli, F., Carella, A.M., Pogliani, E., Liberati, A.M., Dammacco, F., Ciccone, G. & Boccadoro, M. (2004) Intermediate-dose melphalan improves survival of myeloma patients aged 50 to 70: results of a randomized controlled trial. *Blood,* **104,** 3052-3057.

Palumbo, A., Bringhen, S., Caravita, T., Merla, E., Capparella, V., Callea, V., Cangialosi, C., Grasso, M., Rossini, F., Galli, M., Catalano, L., Zamagni, E., Petrucci, M.T., De Stefano, V., Ceccarelli, M., Ambrosini, M.T., Avonto, I., Falco, P., Ciccone, G., Liberati, A.M., Musto, P. & Boccadoro, M. (2006) Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. *Lancet,* **367,** 825-831.

Palumbo, A., Falco, P., Corradini, P., Falcone, A., Di Raimondo, F., Giuliani, N., Crippa, C., Ciccone, G., Omede, P., Ambrosini, M.T., Gay, F., Bringhen, S., Musto, P., Foa, R., Knight, R., Zeldis, J.B., Boccadoro, M. & Petrucci, M.T. (2007) Melphalan, prednisone, and lenalidomide treatment for newly diagnosed myeloma: a report from the GIMEMA-Italian Multiple Myeloma Network. *Journal of Clinical Oncology,* **25,** 4459-4465.

Palumbo, A., Bringhen, S., Liberati, A.M., Caravita, T., Falcone, A., V., C., Montanaro, M., Ria, R., Capaldi, A., Zambello, R., Benevolo, G., Derudas, D., Dore, F., Cavallo, F., Gay, F., Falco, P., Ciccone, G., Musto, P., Cavo, M. & Boccadoro, M. (2008a) Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: updated results of a randomized controlled trial. *Blood,* **112,** 3107-3114.

Palumbo, A., Rajkumar, S.V., Dimopoulos, M.A., Richardson, P.G., San Miguel, J., Barlogie, B., Harousseau, J., Zonder, J.A., Cavo, M., Zangari, M., Attal, M., Belch, A., Knop, S., Joshua, D., Sezer, O., Ludwig, H., Vesole, D., Bladé, J., Kyle, R., Westin, J., Weber, D., Bringhen, S., Niesvizky, R., Waage, A., von Lilienfeld-Toal, M., Lonial, S., Morgan, G.J., Orlowski, R.Z., Shimizu, K., Anderson, K.C., Boccadoro, M., Durie, B.G., Sonneveld, P. & Hussein, M.A. (2008b) Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. *Leukemia,* **22,** 414-423.

Palumbo, A., Dimopoulos, M.A., Delforge, M., Kropff, M., Foa, R., Yu, Z., Herbein, L., Mei, J., Jacques, C. & Catalano, J. (2009) A phase III study to determine the efficacy and safety of lenalidomide in combination with melphalan and prednisone (MPR) in elderly patients with newly diagnosed multiple myeloma. . *Blood (ASH Annual Meeting Abstracts),* **114,** Abstract 613.

Palumbo, A.P., Gay, F., Falco, P., Crippa, C., Montefusco, V., Patriarca, F., Rossini, F., Caltagirone, S., Benevolo, G., Pescosta, N., Guglielmelli, T., Bringhen, S., Offidani, M., Giuliani, N., Petrucci, M.T., Musto, P., Liberati, A.M., Rossi, G., Corradini, P. &

Boccadoro, M. (2010) Bortezomib as induction before autologous transplantation, followed by lenalidomide as consolidation-maintenance in untreated multiple myeloma patients. *Journal of Clinical Oncology,* **28,** 800-807.

Penfield, J.G. (2006) Multiple myeloma in end-stage renal disease. *Seminars in Dialysis,* **19,** 329-334.

Perez-Persona, E., Vidriales, M.B., Mateo, G., Garcia-Sanz, R., Mateos, M.V., de Coca, A.G., Galende, J., Martin-Nunez, G., Alonso, J.M., de Las Heras, N., Hernandez, J.M., Martin, A., Lopez-Berges, C., Orfao, A. & San Miguel, J.F. (2007) New criteria to identify risk of progression in monoclonal gammopathy of uncertain significance and smoldering multiple myeloma based on multiparameter flow cytometry analysis of bone marrow plasma cells. *Blood,* **110**, 2586-2592.

Perez-Simon, J.A., Martino, R., Alegre, A., Tomas, J.F., De Leon, A., Caballero, D., Sureda, A., Sierra, J. & San Miguel, J.F. (2003) Chronic but not acute graft-versus-host disease improves outcome in multiple myeloma patients after non-myeloablative allogeneic transplantation. *British Journal of Haematology,* **121**, 104-108.

Pönisch, W., Rozanski, M., Goldschmidt, H., Hoffmann, F.A., Boldt, T., Schwarzer, A., Ritter, U., Rohrberg, R., Schwalbe, E., Uhlig, J., Zehrfeld, T., Schirmer, V., Haas, A., Kreibich, U., Niederwieser, D.; East German Study Group of Haematology and Oncology (OSHO) (2008) Combined bendamustine, prednisolone and thalidomide for refractory or relapsed multiple myeloma after autologous stem-cell transplantation or conventional chemotherapy: results of a Phase I clinical trial. *British Journal of Haematology*, **143**:191-200.

Pratt, G. (2008) The evolving use of serum free light chain assays in haematology. *British Journal of Haematology,* **141,** 413-422.

Raab, M.S., Breitkreutz, I., Hundemer, M., Benner, A., Klaus, J., Hegenbart, U., Moehler, T., Ho, A.D., Zeier, M. & Goldschmidt, H. (2006) The outcome of autologous stem cell transplantation in patients with plasma cell disorders and dialysis-dependent renal failure. *Haematologica,* **91,** 1555-1558.

Rades, D., Hoskin, P.J., Stalpers, L.J., Schulte, R., Poortmans, P., Veninga, T., Dahm-Daphi, J., Obralic, N., Wildfang, I., Bahrehmand, R., Engenhart-Cabilic, R. & Schild, S.E. (2006) Short-course radiotherapy is not optimal for spinal cord compression due to myeloma. *International Journal of Radiation Oncology Biology Physics,* **64,** 1452-1457.

Rajkumar, S.V., Hayman, S.R., Lacy, M.Q., Dispenzieri, A., Geyer, S.M., Kabat, B., Zeldenrust, S.R., Kumar, S., Greipp, P.R., Fonseca, R., Lust, J.A., Russell, S.J., Kyle, R.A., Witzig, T.E. & Gertz, M.A. (2005) Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. *Blood,* **106,** 4050-4053.

Rajkumar, S.V., Blood, E., Vesole, D., Fonseca, R. & Greipp, P.R. (2006) Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. *Journal of Clinical Oncology,* **24,** 431-436.

Rajkumar, S.V., Rosinol, L., Hussein, M., Catalano, J., Jedrzejczak, W., Lucy, L., Olesnyckyj, M., Yu, Z., Knight, R., Zeldis, J.B. & Blade, J. (2008) Multicenter, randomized, double-blind, placebo-controlled study of thalidomide plus dexamethasone compared with dexamethasone as initial therapy for newly diagnosed multiple myeloma. *Journal of Clinical Oncology,* **26,** 2171-2177.

Rajkumar, S.V., Jacobus, S., Callander, N.S., Fonseca, R., Vesole, D.H., Williams, M.E., Abonour, R., Siegel, D.S., Katz, M. & Greipp, P.R. (2010) Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. *Lancet Oncology,* **11,** 29-37.

Rajkumar, S.V., Harousseau, J.L., Durie, B., Anderson, K.C., Dimopoulos, M., Kyle, R., Blade, J., Richardson, P., Orlowski, R., Siegel, D., Jagannath, S., Facon, T., Avet-Loiseau, H.,

Lonial, S., Palumbo, A., Zonder, J., Ludwig, H., Vesole, D., Sezer, O., Munshi, N.C. and Miguel, J.S. (2011) Guidelines for the Uniform Reporting of Clinical Trials: Report of the 2009 International Myeloma Workshop Consensus Panel I. *Blood,* in press.

Rawstron, A.C., Orfao, A., Beksac, M., Bezdickova, L., Brooimans, R.A., Bumbea, H., Dalva, K., Fuhler, G., Gratama, J., Hose, D., Kovarova, L., Lioznov, M., Mateo, G., Morilla, R., Mylin, A.K., Omede, P., Pellat-Deceunynck, C., Perez Andres, M., Petrucci, M., Ruggeri, M., Rymkiewicz, G., Schmitz, A., Schreder, M., Seynaeve, C., Spacek, M., de Tute, R.M., Van Valckenborgh, E., Weston-Bell, N., Owen, R.G., San Miguel, J.F., Sonneveld, P. & Johnsen, H.E. (2008) Report of the European Myeloma Network on multiparametric flow cytometry in multiple myeloma and related disorders. *Haematologica,* **93,** 431-438.

Reece, D.E., Bredeson, C., Perez, W.S., Jagannath, S., Zhang, M.J., Ballen, K.K., Elfenbein, G.J., Freytes, C.O., Gale, R.P., Gertz, M.A., Gibson, J., Giralt, S.A., Keating, A., Kyle, R.A., Maharaj, D., Marcellus, D., McCarthy, P.L., Milone, G.A., Nimer, S.D., Pavlovsky, S., To, L.B., Weisdorf, D.J., Wiernik, P.H., Wingard, J.R. & Vesole, D.H. (2003) Autologous stem cell transplantation in multiple myeloma patients <60 vs >/=60 years of age. *Bone Marrow Transplantation,* **32,** 1135-1143.

Reece, D.E., Flomenberg, N., Badros, A., Phillips, G.L., Filicko, J., Howard, D.S., Meisenberg, B., Rapoport, A., Vesole, D.H. (2006) Update of melphalan 280 mg/m2 plus amifostine cytoprotection before autologous stem cell transplantation as part of initial therapy in multiple myeloma patients. *Journal of Clinical Oncology, 2006 ASCO Annual Meeting Proceedings Part I,* **24,** 7608.

Reeder, C.B., Reece, D.E., Kukreti, V., Chen, C., Trudel, S., Hentz, J., Noble, B., Pirooz, N.A., Spong, J.E., Piza, J.G., Zepeda, V.H., Mikhael, J.R., Leis, J.F., Bergsagel, P.L., Fonseca, R. & Stewart, A.K. (2009) Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial. *Leukemia,* **23,** 1337-1341.

Riccardi, A., Mora, O., Tinelli, C., Valentini, D., Brugnatelli, S., Spanedda, R., De Paoli, A., Barbarano, L., Di Stasi, M., Giordano, M., Delfini, C., Nicoletti, G., Bergonzi, C., Rinaldi, E., Piccinini, L. & Ascari, E. (2000) Long-term survival of stage I multiple myeloma given chemotherapy just after diagnosis or at progression of the disease: a multicentre randomized study. Cooperative Group of Study and Treatment of Multiple Myeloma. *British Journal of Cancer,* **82,** 1254-1260.

Richardson, P.G., Schlossman, R.L., Weller, E., Hideshima, T., Mitsiades, C., Davies, F., LeBlanc, R., Catley, L.P., Doss, D., Kelly, K., McKenney, M., Mechlowicz, J., Freeman, A., Deocampo, R., Rich, R., Ryoo, J.J., Chauhan, D., Balinski, K., Zeldis, J. & Anderson, K.C. (2002) Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma. *Blood,* **100,** 3063-3067.

Richardson, P.G., Barlogie, B., Berenson, J., Singhal, S., Jagannath, S., Irwin, D., Rajkumar, S.V., Srkalovic, G., Alsina, M., Alexanian, R., Siegel, D., Orlowski, R.Z., Kuter, D., Limentani, S.A., Lee, S., Hideshima, T., Esseltine, D.L., Kauffman, M., Adams, J., Schenkein, D.P. & Anderson, K.C. (2003) A phase 2 study of bortezomib in relapsed, refractory myeloma. *New England Journal of Medicine,* **348,** 2609-2617.

Richardson, P.G., Sonneveld, P., Schuster, M.W., Irwin, D., Stadtmauer, E.A., Facon, T., Harousseau, J.L., Ben-Yehuda, D., Lonial, S., Goldschmidt, H., Reece, D., San-Miguel, J.F., Blade, J., Boccadoro, M., Cavenagh, J., Dalton, W.S., Boral, A.L., Esseltine, D.L., Porter, J.B., Schenkein, D. & Anderson, K.C. (2005) Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *New England Journal of Medicine,* **352,** 2487-2498.

Richardson, P.G., Blood, E., Mitsiades, C.S., Jagannath, S., Zeldenrust, S.R., Alsina, M., Schlossman, R.L., Rajkumar, S.V., Desikan, K.R., Hideshima, T., Munshi, N.C., Kelly-Colson, K., Doss, D., McKenney, M.L., Gorelik, S., Warren, D., Freeman, A., Rich, R.,

Wu, A., Olesnyckyj, M., Wride, K., Dalton, W.S., Zeldis, J., Knight, R., Weller, E. & Anderson, K.C. (2006) A randomized phase 2 study of lenalidomide therapy for patients with relapsed or relapsed and refractory multiple myeloma. *Blood,* **108,** 3458-3464.

Richardson, P.G., Sonneveld, P., Schuster, M., Irwin, D., Stadtmauer, E., Facon, T., Harousseau, J.L., Ben-Yehuda, D., Lonial, S., Goldschmidt, H., Reece, D., Miguel, J.S., Blade, J., Boccadoro, M., Cavenagh, J., Alsina, M., Rajkumar, S.V., Lacy, M., Jakubowiak, A., Dalton, W., Boral, A., Esseltine, D.L., Schenkein, D. & Anderson, K.C. (2007) Extended follow-up of a phase 3 trial in relapsed multiple myeloma: final time-to-event results of the APEX trial. *Blood,* **110,** 3557-3560.

Richardson, P.G., Lonial, S., Jakubowiak, A.J., Jagannath, S., Raje, N.S., Avigan, D.E., Ghobrial, I., Schlossman, R.L., Mazumder, A., Munshi, N.C., Laubach, J., Vesole, D., Joyce, R., Rosenblatt, J., Xie, W., Doss, D., Warren, D.L., Ittleman, K., Revta, C., Francis, D., Leister, C., Kaster, S., Delaney, C., Lauria, M., Mitsiades, C.S., Hideshima, T., Knight, R., Esseltine, D.-L., Weller, E. & Anderson, K.C. (2009) High response rates and encouraging time-to-event data with lenalidomide, bortezomib, and dexamethasone in newly diagnosed multiple myeloma: final results of a phase I/II study. *Blood (ASH Annual Meeting Abstracts),* **114,** Abstract 1218.

Rosen, L.S., Gordon, D., Kaminski, M., Howell, A., Belch, A., Mackey, J., Apffelstaedt, J., Hussein, M., Coleman, R.E., Reitsma, D.J., Seaman, J.J., Chen, B.L. & Ambros, Y. (2001) Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. *Cancer Journal,* **7,** 377-387.

Rosen, L.S., Gordon, D., Kaminski, M., Howell, A., Belch, A., Mackey, J., Apffelstaedt, J., Hussein, M.A., Coleman, R.E., Reitsma, D.J., Chen, B.L. & Seaman, J.J. (2003) Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. *Cancer,* **98,** 1735-1744.

Rosiñol, L., Oriol, A., Mateos, M.V., Sureda, A., Garcia-Sanchez, P., Gutierrez, N., Alegre, A., Lahuerta, J.J., de la Rubia, J., Herrero, C., Liu, X., Van de Velde, H., San Miguel, J. & Blade, J. (2007) Phase II PETHEMA trial of alternating bortezomib and dexamethasone as induction regimen before autologous stem-cell transplantation in younger patients with multiple myeloma: efficacy and clinical implications of tumor response kinetics. *Journal of Clinical Oncology,* **25,** 4452-4458.

Rosiñol, L., Pérez-Simón, J.A., Sureda, A., de la Rubia, J., de Arriba, F., Lahuerta, J.J., González, J.D., Díaz-Mediavilla, J., Hernández, B., García-Frade, J., Carrera, D., León, A., Hernández, M., Abellán, P.F., Bergua, J.M., San Miguel, J. & Bladé, J. (2008) A prospective PETHEMA study of tandem autologous transplantation versus autograft followed by reduced-intensity conditioning allogeneic transplantation in newly diagnosed multiple myeloma. *Blood,* **112,** 3591-3593.

Rosiñol, L., Cibeira, M.T., Martinez, J., Mateos, M.V., Oriol, A., Terol, M.J., García-Laraña, J., Hernández, D., Rubia, J.d.l., Sureda, A., Besalduch, J., Palomera, L., Gonzalez, Y., Echebeste, M.A., Díaz-Mediavilla, J., Arriba, F.d., Alegre, A., Hernández, M.T., Lahuerta, J.J., Miguel, J.F.F.S. & Blade, J. (2009) Thalidomide / dexamethasone (TD) vs. bortezomib (velcade)â/thalidomide / dexamethasone (VTD) vs. VBMCP/VBAD/velcadeâ as induction regimens prior autologous stem cell transplantation (ASCT) in multiple myeloma (MM): Results of a phase III PETHEMA/GEM trial. *Blood (ASH Annual Meeting Abstracts),* **114,** Abstract 130.

Rotta, M., Storer, B.E., Sahebi, F., Shizuru, J.A., Bruno, B., Lange, T., Agura, E.D., McSweeney, P.A., Pulsipher, M.A., Hari, P., Maziarz, R.T., Chauncey, T.R., Appelbaum, F.R., Sorror, M.L., Bensinger, W., Sandmaier, B.M., Storb, R.F. & Maloney, D.G. (2009) Long-term

outcome of patients with multiple myeloma after autologous hematopoietic cell transplantation and nonmyeloablative allografting. *Blood,* **113,** 3383-3391.

Roussel, M., Moreau, P., Huynh, A., Mary, J.Y., Danho, C., Caillot, D., Hulin, C., Fruchart, C., Marit, G., Pégourié, B., Lenain, P., Araujo, C., Kolb, B., Randriamalala, E., Royer, B., Stoppa, A.M., Dib, M., Dorvaux, V., Garderet, L., Mathiot, C., Avet-Loiseau, H., Harousseau, J.L. & Attal, M. (2010) Bortezomib and high-dose melphalan as conditioning regimen before autologous stem cell transplantation in patients with de novo multiple myeloma: a phase 2 study of the Intergroupe Francophone du Myelome (IFM). *Blood,* **115,** 32-37.

Roussou, M., Kastritis, E., Migkou, M., Psimenou, E., Grapsa, I., Matsouka, C., Barmparousi, D., Terpos, E. & Dimopoulos, M.A. (2008) Treatment of patients with multiple myeloma complicated by renal failure with bortezomib-based regimens. *Leukemia and Lymphoma,* 49, 890-895.

Samson, D., Gaminara, E., Newland, A., Van de Pette, J., Kearney, J., McCarthy, D., Joyner, M., Aston, L., Mitchell, T. & Hamon, M. (1989) Infusion of vincristine and doxorubicin with oral dexamethasone as first-line therapy for multiple myeloma. *Lancet,* **2,** 882-885.

San-Miguel, J.F. & Mateos, M.V. (2009) How to treat a newly diagnosed young patient with multiple myeloma. Hematology 2009: American Society of Hematology Education Program Program Book, 555-65.

San Miguel, J.F., Lahuerta, J.J., Garcia-Sanz, R., Alegre, A., Blade, J., Martinez, R., Garcia-Larana, J., De La Rubia, J., Sureda, A., Vidal, M.J., Escudero, A., Perez-Esquiza, E., Conde, E., Garcia-Ruiz, J.C., Cabrera, R., Caballero, D., Moraleda, J.M., Leon, A., Besalduch, J., Hernandez, M.T., Rifon, J., Hernandez, F., Solano, C., Palomera, L., Parody, R., Gonzalez, J.D., Mataix, R., Maldonado, J., Constela, J., Carrera, D., Bello, J.L., De Pablos, J.M., Perez-Simon, J.A., Torres, J.P., Olanguren, J., Prieto, E., Acebede, G., Penarrubia, M.J., Torres, P., Diez-Martin, J.L., Rivas, A., Sanchez, J.M. & Diaz-Mediavilla, J. (2000) Are myeloma patients with renal failure candidates for autologous stem cell transplantation? *Hematology Journal,* **1,** 28-36.

San Miguel, J., Harousseau, J.L., Joshua, D. & Anderson, K.C. (2008a) Individualizing treatment of patients with myeloma in the era of novel agents. *Journal of Clinical Oncology,* **26,** 2761-2766.

San Miguel, J.F., Schlag, R., Khuageva, N.K., Dimopoulos, M.A., Shpilberg, O., Kropff, M., Spicka, I., Petrucci, M.T., Palumbo, A., Samoilova, O.S., Dmoszynska, A., Abdulkadyrov, K.M., Schots, R., Jiang, B., Mateos, M.V., Anderson, K.C., Esseltine, D.L., Liu, K., Cakana, A., van de Velde, H. & Richardson, P.G. (2008b) Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *New England Journal of Medicine,* **359,** 906-917.

San Miguel, J.F., Richardson, P.G., Sonneveld, P., Schuster, M.W., Irwin, D., Stadtmauer, E.A., Facon, T., Harousseau, J.L., Ben-Yehuda, D., Lonial, S., Goldschmidt, H., Reece, D., Blade, J., Boccadoro, M., Cavenagh, J.D., Neuwirth, R., Boral, A.L., Esseltine, D.L. & Anderson, K.C. (2008c) Efficacy and safety of bortezomib in patients with renal impairment: results from the APEX phase 3 study. *Leukemia,* **22,** 842-849.

Schaar, C.G., Kluin-Nelemans, H.C., Te Marvelde, C., le Cessie, S., Breed, W.P., Fibbe, W.E., van Deijk, W.A., Fickers, M.M., Roozendaal, K.J. & Wijermans, P.W. (2005) Interferon-alpha as maintenance therapy in patients with multiple myeloma. *Annals of Oncology,* **16,** 634-639.

Shaughnessy, J.D., Jr., Zhan, F., Burington, B.E., Huang, Y., Colla, S., Hanamura, I., Stewart, J.P., Kordsmeier, B., Randolph, C., Williams, D.R., Xiao, Y., Xu, H., Epstein, J., Anaissie, E., Krishna, S.G., Cottler-Fox, M., Hollmig, K., Mohiuddin, A., Pineda-Roman, M., Tricot, G., van Rhee, F., Sawyer, J., Alsayed, Y., Walker, R., Zangari, M., Crowley, J. & Barlogie, B. (2007) A validated gene expression model of high-risk multiple myeloma is defined

by deregulated expression of genes mapping to chromosome 1. *Blood,* **109,** 2276-2284.

Shaw, B.E., Peggs, K., Bird, J.M., Cavenagh, J., Hunter, A., Alejandro Madrigal, J., Russell, N.H., Sirohi, B., Towlson, K., Williams, C.D. & Marks, D.I. (2003) The outcome of unrelated donor stem cell transplantation for patients with multiple myeloma. *British Journal of Haematology,* **123,** 886-895.

Shustik, C., Belch, A., Robinson, S., Rubin, S.H., Dolan, S.P., Kovacs, M.J., Grewal, K.S., Walde, D., Barr, R., Wilson, J., Gill, K., Vickars, L., Rudinskas, L., Sicheri, D.A., Wilson, K., Djurfeldt, M., Shepherd, L.E., Ding, K. & Meyer, R.M. (2007) A randomised comparison of melphalan with prednisone or dexamethasone as induction therapy and dexamethasone or observation as maintenance therapy in multiple myeloma: NCIC CTG MY.7. *British Journal of Haematology,* **136,** 203-211.

Sidra, G., Williams, C.D., Russell, N.H., Zaman, S., Myers, B. & Byrne, J.L. (2006) Combination chemotherapy with cyclophosphamide, thalidomide and dexamethasone for patients with refractory, newly diagnosed or relapsed myeloma. *Haematologica,* **91,** 862-863.

Siegel, D.S., Desikan, K.R., Mehta, J., Singhal, S., Fassas, A., Munshi, N., Anaissie, E., Naucke, S., Ayers, D., Spoon, D., Vesole, D., Tricot, G. & Barlogie, B. (1999) Age is not a prognostic variable with autotransplants for multiple myeloma. *Blood,* **93,** 51-54.

Sinclair, D. (2002) IgD myeloma: clinical, biological and laboratory features. *Clinical Laboratory,* **48,** 617-622.

Sirohi, B., Powles, R., Mehta, J., Treleaven, J., Raje, N., Kulkarni, S., Rudin, C., Bhagwati, N., Horton, C., Saso, R., Singhal, S. & Parikh, R. (2001) The implication of compromised renal function at presentation in myeloma: similar outcome in patients who receive high-dose therapy: a single-center study of 251 previously untreated patients. *Medical Oncology,* **18,** 39-50.

Smith, A., Wisloff, F. & Samson, D. (2006) Guidelines on the diagnosis and management of multiple myeloma 2005. *British Journal of Haematology,* **132,** 410-451.

Snowden JA, Ahmedzai SH, Ashcroft J, D'Sa S, Littlewood T, Low E, Lucraft H, Maclean R, Feyler S, Pratt G, Bird JM, on behalf of the Haemato-oncology Task Force of the British Committee for Standards in Haematology and UK Myeloma Forum (2011) Guidelines for supportive care in multiple myeloma 2011. *British Journal of Haematology, in press*

Sonneveld, P., van der Holt, B., Schmidt-Wolf, I.G.H., Bertsch, U., el Jarari, L., Salwender, H.-J., Zweegman, S., Vellenga, E., Schubert, J., Blau, I.W., Jie, G., Beverloo, B., Jauch, A., Hose, D., Schaafsma, R., Kersten, M.J., Delforge, M., de Weerdt, O., van der Griend, R., Wijermans, P.W., Martin, H., van der Velde, H., Lokhorst, H.M. & Goldschmidt, H. (2008) First analysis of HOVON-65/GMMG-HD4 randomized phase III trial comparing bortezomib, adriamycine, dexamethasone (PAD) vs VAD as induction treatment prior to high dose melphalan (HDM) in patients with newly diagnosed multiple myeloma (MM). *Blood (ASH Annual Meeting Abstracts),* **112,** Abstract 653.

Spencer, A., Prince, H.M., Roberts, A.W., Prosser, I.W., Bradstock, K.F., Coyle, L., Gill, D.S., Horvath, N., Reynolds, J. & Kennedy, N. (2009) Consolidation therapy with low-dose thalidomide and prednisolone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell transplantation procedure. *Journal of Clinical Oncology,* **27,** 1788-1793.

Srkalovic, G., Cameron, M.G., Rybicki, L., Deitcher, S.R., Kattke-Marchant, K. & Hussein, M.A. (2004) Monoclonal gammopathy of undetermined significance and multiple myeloma are associated with an increased incidence of venothromboembolic disease. *Cancer,* **101,** 558-666.

Stadtmauer, E.A., Weber, D.M., Niesvizky, R., Belch, A., Prince, M.H., San Miguel, J.F., Facon, T., Olesnyckyj, M., Yu, Z., Zeldis, J.B., Knight, R.D. & Dimopoulos, M.A. (2009) Lenalidomide in combination with dexamethasone at first relapse in comparison with

its use as later salvage therapy in relapsed or refractory multiple myeloma. *European Journal of Haematology,* **82,** 426-432.

Stewart, A.K., Vescio, R., Schiller, G., Ballester, O., Noga, S., Rugo, H., Freytes, C., Stadtmauer, E., Tarantolo, S., Sahebi, F., Stiff, P., Meharchard, J., Schlossman, R., Brown, R., Tully, H., Benyunes, M., Jacobs, C., Berenson, R., White, M., DiPersio, J., Anderson, K.C. & Berenson, J. (2001) Purging of autologous peripheral-blood stem cells using CD34 selection does not improve overall or progression-free survival after high-dose chemotherapy for multiple myeloma: results of a multicenter randomized controlled trial. *Journal of Clinical Oncology,* **19,** 3771-3779.

Stewart, A.K., Chen, C.I., Howson-Jan, K., White, D., Roy, J., Kovacs, M.J., Shustik, C., Sadura, A., Shepherd, L., Ding, K., Meyer, R.M. & Belch, A.R. (2004) Results of a multicenter randomized phase II trial of thalidomide and prednisone maintenance therapy for multiple myeloma after autologous stem cell transplant. *Clinical Cancer Research,* **10,** 8170-8176.

Stewart, A.K., Bergsagel, P.L., Greipp, P.R., Dispenzieri, A., Gertz, M.A., Hayman, S.R., Kumar, S., Lacy, M.Q., Lust, J.A., Russell, S.J., Witzig, T.E., Zeldenrust, S.R., Dingli, D., Reeder, C.B., Roy, V., Kyle, R.A., Rajkumar, S.V. & Fonseca, R. (2007) A practical guide to defining high-risk myeloma for clinical trials, patient counseling and choice of therapy. *Leukemia,* **21,** 529-534.

Terpos, E. & Dimopoulos, M.A. (2005) Myeloma bone disease: pathophysiology and management. *Annals of Oncology,* **16,** 1223-1231.

Terpos, E. & Rahemtulla, A. (2004) Bisphosphonate treatment for multiple myeloma. *Drugs Today (Barc),* **40,** 29-40.

Terpos, E., Sezer, O., Croucher, P.I., García-Sanz, R., Boccadoro, M., San Miguel, J., Ashcroft, J., Bladé, J., Cavo, M., Delforge, M., Dimopoulos, M.A., Facon, T., Macro, M., Waage, A. & Sonneveld, P. (2009) The use of bisphosphonates in multiple myeloma: recommendations of an expert panel on behalf of the European Myeloma Network. *Annals of Oncology,* **20,** 1303-1317.

Tosi, P., Zamagni, E., Cellini, C., Cangini, D., Tacchetti, P., Tura, S., Baccarani, M. & Cavo, M. (2004) Thalidomide alone or in combination with dexamethasone in patients with advanced, relapsed or refractory multiple myeloma and renal failure. *European Journal of Haematology,* **73,** 98-103.

Tosi, P., Zamagni, E., Cellini, C., Plasmati, R., Cangini, D., Tacchetti, P., Perrone, G., Pastorelli, F., Tura, S., Baccarani, M. & Cavo, M. (2005) Neurological toxicity of long-term (>1 yr) thalidomide therapy in patients with multiple myeloma. *European Journal of Haematology,* **74,** 212-216.

van de Velde, H.J., Liu, X., Chen, G., Cakana, A., Deraedt, W. & Bayssas, M. (2007) Complete response correlates with long-term survival and progression-free survival in high-dose therapy in multiple myeloma. *Haematologica,* **92,** 1399-1406.

Vela-Ojeda, J., Garcia-Ruiz-Esparza, M.A., Padilla-Gonzalez, Y., Gomez-Almaguer, D., Gutierrez-Aguirre, C.H., Gomez-Rangel, D., Morales-Toquero, A., Ruiz-Delgado, G.J., Delgado-Lamas, J.L. & Ruiz-Arguelles, G.J. (2007) Autologous peripheral blood stem cell transplantation in multiple myeloma using oral versus I.V. melphalan. *Annals of Hematology,* **86,** 277-282.

Vigneau, C., Ardiet, C., Bret, M., Laville, M., Fiere, D., Tranchand, B. & Fouque, D. (2002) Intermediate-dose (25mg/m2) IV melphalan for multiple myeloma with renal failure. *Journal of Nephrology,* **15,** 684-689.

Vogel, C.L., Yanagihara, R.H., Wood, A.J., Schnell, F.M., Henderson, C., Kaplan, B.H., Purdy, M.H., Orlowski, R., Decker, J.L., Lacerna, L. & Hohneker, J.A. (2004) Safety and pain palliation of zoledronic acid in patients with breast cancer, prostate cancer, or multiple myeloma who previously received bisphosphonate therapy. *Oncologist,* **9,** 687-695.

Waage, A., Gimsing, P., Juliusson, G., Turesson, I., Gulbrandsen, N., Eriksson, T., Hjorth, M., Nielsen, J.L., Lenhoff, S., Westin, J. & Wisloff, F. (2004) Early response predicts thalidomide efficiency in patients with advanced multiple myeloma. *British Journal of Haematology,* **125,** 149-155.

Wang, M., Knight, R., Dimopoulos, M., Siegel, D., Rajkumar, S.V., Facon, T., Alexanian, R., Yu, Z., Zeldis, J., Olesnyckyj, M. & Weber, D. (2006) Lenalidomide in combination with dexamethasone was more effective than dexamethasone in patients who have received prior thalidomide for relapsed or refractory multiple myeloma. *Blood (ASH Annual Meeting Abstracts),* **108,** Abstract 3553.

Weber, D.M., Gavino, M., Delasalle, K., Rankin, K., Giralt, S., Alexanian, R. (1999) Thalidomide alone or with dexamethasone for multiple myeloma. *Blood,* **94 (Suppl. 1),** 604a.

Weber, D., Wang, M., Chen, C., Belch, A., Stadtmauer, E.A., Niesvisky, R., Yu, Z., Olesnyckyj, M., Zeldis, J., Knight, R.D. & Dimopoulos, M. (2006) Lenalidomide Plus High-Dose Dexamethasone Provides Improved Overall Survival Compared to High-Dose Dexamethasone Alone for Relapsed or Refractory Multiple Myeloma (MM): Results of 2 Phase III Studies (MM-009, MM-010) and Subgroup Analysis of Patients with Impaired Renal Function. *Blood (ASH Annual Meeting Abstracts),* **108,** 3547.

Weber, D.M., Chen, C., Niesvizky, R., Wang, M., Belch, A., Stadtmauer, E.A., Siegel, D., Borrello, I., Rajkumar, S.V., Chanan-Khan, A.A., Lonial, S., Yu, Z., Patin, J., Olesnyckyj, M., Zeldis, J.B. & Knight, R.D. (2007) Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *New England Journal of Medicine,* **357,** 2133-2142.

Wechalekar, A., Amato, D., Chen, C., Stewart K., A. & Reece, D. (2005) IgD multiple myeloma--a clinical profile and outcome with chemotherapy and autologous stem cell transplantation. *Annals of Hematology,* **84,** 115-117.

Wijermans, P., Schaafsma, M., Norden, Y.v., Ammerlaan, R., Wittebol, S., Sinnige, H., Zweegman, S., Kooi, M.v.M., Griend, R.V.d., Lokhorst, H. & Sonneveld, P. (2008) Melphalan/prednisone versus melphalan/prednisone/thalidomide in induction therapy for multiple myeloma in elderly patients: final analysis of the dutch cooperative group HOVON 49 study. *Blood (ASH Annual Meeting Abstracts),* **112,** Abstract 649.

Zervas, K., Mihou, D., Katodritou, E., Pouli, A., Mitsouli, C.H., Anagnostopoulos, A., Delibasi, S., Kyrtsonis, M.C., Anagnostopoulos, N., Terpos, E., Zikos, P., Maniatis, A. & Dimopoulos, M.A. (2007) VAD-doxil versus VAD-doxil plus thalidomide as initial treatment for multiple myeloma: results of a multicenter randomized trial of the Greek Myeloma Study Group. *Annals of Oncology,* **18,** 1369-1375.

Zucchelli, P., Pasquali, S., Cagnoli, L. & Ferrari, G. (1988) Controlled plasma exchange trial in acute renal failure due to multiple myeloma. *Kidney International,* **33,** 1175-1180.

Table 1 - Initial investigations in patients with myeloma

Screening tests	Tests to establish diagnosis	Tests to estimate tumour burden and prognosis	Tests to assess myeloma-related organ impairment (ROTI)	Special tests indicated in some patients
FBC, ESR or plasma viscosity	Bone marrow aspirate + trephine biopsy with plasma cell phenotyping	FISH analysis	FBC	
Urea, creatinine, calcium, albumin Electrophoresis of serum and concentrated urine Quantification of non-isotypic immunoglobulins	Immunofixation of serum and urine	Quantification of Monoclonal protein in serum and urine Albumin B2-microglobulin	Serum urea and creatinine Creatinine clearance (measured or calculated) Calcium Albumin Plasma viscosity Tissue biopsy (or fat pad aspirate) for amyloid (if suspected) Quantification of non-isotypic immunoglobulins	SFLC assay in oligo-secretory, light chain only and non-secretory disease
X-ray of symptomatic areas	Skeletal survey	Skeletal survey	Skeletal survey	MRI CT scan

FBC, full blood count; ESR, erythrocyte sedimentation rate; FISH, Fluorescence *in situ* hybridization; SFLC, serum-free light chain; MRI, Magnetic resonance imaging; CT, Computerized tomography.

Table 2- Diagnostic criteria for MGUS, asymptomatic myeloma and symptomatic myeloma (adapted from International Myeloma Working Group, 2003)

MGUS	**Asymptomatic myeloma**	**Symptomatic myeloma**
M-protein in serum <30 g/l	M-protein in serum ≥30 g/l and/or	M-protein in serum and/or urine**
Bone marrow clonal plasma cells <10 % and low level of plasma cell infiltration in a trephine biopsy (if done)	Bone marrow clonal plasma cells ≥10 %	Bone marrow (clonal) plasma cells* or biopsy proven plasmacytoma
No related organ or tissue impairment ((no end organ damage including bone lesions)	No related organ or tissue impairment (no end organ damage including bone lesions) or symptoms	Myeloma-related organ or tissue impairment (including bone lesions)

*If flow cytometry is performed, most plasma cells (> 90%) will show a 'neoplastic' phenotype.
Some patients may have no symptoms but have related organ or tissue impairment.

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

Table 3 - Myeloma-related organ or tissue impairment (ROTI) (adapted from International Myeloma Working Group, 2003)

Clinical effects due to myeloma	Definition
*Increased calcium levels	Corrected serum calcium >0.25 mmol/l above the upper limit of normal or >2.75 mmol/l
*Renal insufficiency	Creatinine>173 µmol/l
*Anaemia	Haemoglobin 20 g/l below the lower limit of normal or haemoglobin <100 g/l
*Bone lesions	Lytic lesions or osteoporosis with compression fractures (MRI or CT may clarify)
Other	Symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (> 2 episodes in 12 months)

*CRAB (calcium, renal insufficiency, anaemia or bone lesions).

MRI, Magnetic resonance imaging; CT, Computerized tomography.

Table 4 - International Staging System (ISS) for multiple myeloma. Adapted from: Greipp, P.R.*et al: Journal of Clinical Oncology,* **23,** 2005, 3412-3420. Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved

Stage	Criteria	Median survival in months
I	Serum $ß_2$ microglobulin < 3.5 mg/l (296 nmol/l) and serum albumin $\geq$ 3.5 g/dl (35g/l or 532 µmol/l)	62 months
II	Neither I or III*	45 months
III	Serum $ß_2$ microglobulin $\geq$ 5.5 mg/l (465 nmol/l)	29 months

Table 5 - International Myeloma Working Group uniform response criteria (Adapted by permission from Macmillan Publishers Ltd: Leukemia: Durie, B.G., Harousseau, J.L., Miguel, J.S., Blade, J., Barlogie, B., Anderson, K., Gertz, M., Dimopoulos, M., Westin, J., Sonneveld, P., Ludwig, H., Gahrton, G., Beksac, M., Crowley, J., Belch, A., Boccadaro, M., Cavo, M., Turesson, I., Joshua, D., Vesole, D., Kyle, R., Alexanian, R., Tricot, G., Attal, M., Merlini, G., Powles, R., Richardson, P., Shimizu, K., Tosi, P., Morgan, G. & Rajkumar, S.V. International uniform response criteria for multiple myeloma. *Leukemia,* 20, 1467-1473., copyright (2006) and Durie, B.G., Harousseau, J.L., Miguel, J.S., Blade, J., Barlogie, B., Anderson, K., Gertz, M., Dimopoulos, M., Westin, J., Sonneveld, P., Ludwig, H., Gahrton, G., Beksac, M., Crowley, J., Belch, A., Boccadaro, M., Cavo, M., Turesson, I., Joshua, D., Vesole, D., Kyle, R., Alexanian, R., Tricot, G., Attal, M., Merlini, G., Powles, R., Richardson, P., Shimizu, K., Tosi, P., Morgan, G. & Rajkumar, S.V. (2006) International uniform response criteria for multiple myeloma. *Leukemia,* 20, 1467-1473. copyright (2009). The latest available data (Rajkumar et *al,* 2011) are also included.

Response sub-category	Response criteria
Stringent complete response (sCR)	CR as defined below plus • Normal SFLC ratio • Absence of phenotypically aberrant plasma cells by multiparameter flow cytometry
Complete response (CR)*	• Negative immunofixation on the serum and urine • Disappearance of any soft tissue plasmacytomas • ≤5% bone marrow plasma cells
Very good partial response (VGPR)*	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis OR • ≥90% reduction in serum M-protein plus reduction in 24-h urinary M-protein by ≥ 90% or to <100 mg/24 h
Partial response (PR)*	• ≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to <200 mg/24 h
Stable disease (SD)	• Not meeting criteria for CR, VGPR, PR or progressive disease

Table 6 - International Myeloma Working Group uniform response criteria: disease progression and relapse (Adapted by permission from Macmillan Publishers Ltd: Leukemia: Durie, B.G., Harousseau, J.L., Miguel, J.S., Blade, J., Barlogie, B., Anderson, K., Gertz, M., Dimopoulos, M., Westin, J., Sonneveld, P., Ludwig, H., Gahrton, G., Beksac, M., Crowley, J., Belch, A., Boccadaro, M., Cavo, M., Turesson, I., Joshua, D., Vesole, D., Kyle, R., Alexanian, R., Tricot, G., Attal, M., Merlini, G., Powles, R., Richardson, P., Shimizu, K., Tosi, P., Morgan, G. & Rajkumar, S.V. International uniform response criteria for multiple myeloma. ***Leukemia,*** 20, **1467-1473., copyright (2006) and Durie, B.G., Harousseau, J.L., Miguel, J.S., Blade, J., Barlogie, B., Anderson, K., Gertz, M., Dimopoulos, M., Westin, J., Sonneveld, P., Ludwig, H., Gahrton, G., Beksac, M., Crowley, J., Belch, A., Boccadaro, M., Cavo, M., Turesson, I., Joshua, D., Vesole, D., Kyle, R., Alexanian, R., Tricot, G., Attal, M., Merlini, G., Powles, R., Richardson, P., Shimizu, K., Tosi, P., Morgan, G. & Rajkumar, S.V. (2006) International uniform response criteria for multiple myeloma.** ***Leukemia,*** **20, 1467-1473. copyright (2009). The latest available data (Rajkumar *et al,* 2011) are also included.**

Relapse subcategory	Relapse criteria
Progressive disease (PD)	Requires at least one of the following – • ≥25% increase in serum M-protein in 3 months (absolute increase must be ≥5g/l) • ≥25% increase in urine M-protein in 3 months (absolute increase must be ≥200 mg/24 h) • ≥25% increase in the difference between involved and uninvolved SFLC levels (applicable only to patients without measurable serum and urine M- protein (absolute increase must be >100 mg/l) • ≥25% increase in bone marrow plasma cell percentage (absolute percentage must be ≥10%) • Development of new bone lesions or soft tissue plasmacytoma • Development of hypercalcaemia
Clinical relapse	Requires at least one of the following – • Development of new bone lesions or soft tissue plasmacytoma • Increase in size of existing plasmacytomas or bone lesions • Any of the following attributable to myeloma: -Development of hypercalcaemia -Development of anaemia (drop in Hb ≥20 g/l) -Rise in serum creatinine

Relapse from CR	Requires at least one of the following – • Reappearance of serum or urine M-protein by immunofixation or electrophoresis • Development of >5% plasma cells in the bone marrow • Appearance of any other sign of progression (eg new plasmacytoma, new lytic bone lesion)

Table 7: Comparison of side effects related to myeloma treatment with novel agents

	Thalidomide	**Bortezomib**	**Lenalidomide**
Neutropenia	No	No	Yes
Thrombocytopenia	No	Yes	Yes
Neuropathy	Yes	Yes	No
Constipation	Yes	Low risk	Low risk
Diarrhoea	No	Yes	No
Somnolence	Yes	No	No
Fatigue	Yes	Yes	Yes
Thrombotic risk	Yes	No	Yes
Route of administration	oral	intravenous	oral

Table 8: Important thalidomide toxicities

- **Venous thromboembolism: highest risk is at diagnosis and when combined with conventional chemotherapy and/or high dose dexamethasone. All patients require a risk assessment to guide thromboprophylaxis (see section 7.3.2)**
- **Sensory peripheral neuropathy: this is common and usually cumulative. It may not resolve for many months following discontinuation of thalidomide. A summary of key recommendations from the supportive care guideline regarding treatment emergent peripheral neuropathy is given in section 7.3.1. Directed questioning, close clinical monitoring and prompt dose reductions if symptoms develop are needed (see Table 11)**
- **Constipation: laxatives are often required pre-emptively**
- **Haematological toxicity is rare and dose reduction is rarely required**
- **Somnolence: evening dosing minimizes this and the effect reduces with use**
- **Rashes: these are varied and may respond to dose reduction. Rarely, Stevens-Johnson syndrome.**
- **Arrhythmias: known cardiac arrhythmias are a relative contra-indication. Consider cardiology review early in symptomatic patients**
- **Thyroid dysfunction: check baseline thyroid function at start of therapy and re-check every 6 months. Patients on thyroxine supplements should have their thyroid function monitored carefully as dosage may change on thalidomide therapy**
- **Congenital malformations due to foetal exposure: there have been no reported cases of birth defects in myeloma patients on thalidomide. Risk management protocols to minimize risks should be followed in all patients including strict contraceptive precautions in both sexes**

Table 9: Important bortezomib toxicities

- **Peripheral neuropathy: predominantly sensory and painful, usually progressive and variably reversible. The incidence, clinical features and risk factors for the development of bortezomib-induced peripheral neuropathy (BIPN) are described in detail in a review by Mohty *et al* (2010). A summary of key recommendations from the supportive care guideline regarding treatment emergent peripheral neuropathy is given in section 7.3.1. It is managed by early detection, dose-reduction (see Table 11) and analgesia Gastrointestinal toxicity: constipation, diarrhoea, abdominal bloating or pain. Patients should be warned of possible symptoms, Severe diarrhoea is relatively rare but occasional patients with severe diarrhoea, unresponsive to loperamide may require admission for hydration as these patients are at risk of developing pre-renal acute renal failure**
- Postural hypotension and pre-syncope secondary to autonomic neuropathy: pre-hydration with saline infusion prior to each dose of bortezomib is a useful prophylactic measure. Screen for pre-syncope and syncope and assess for a postural drop at the start of each treatment cycle. The administration of 500 ml of normal saline prior to each dose of bortezomib may improve tolerance of the drug.
- **Many patients require dose adjustment of their usual anti-hypertensives for the duration of bortezomib therapy**
- **Thrombocytopaenia: usually progressive over 21-day cycle with recovery prior to next cycle. Check full blood count on days 1 and 8; consider dose reduction if platelets <30 x 10^9/l on day 1 and transfuse platelets if <30 x 10^9/l on any other treatment day**
- **Fatigue**

Table 10: Important lenalidomide toxicities

- **Cytopenias: regular blood count monitoring is required (weekly for first 2 courses); patients may need G-CSF**
- **Venous thromboembolism: thromboprophylaxis is recommended (see section 7.3.2 for recommendations)**
- **Constipation**
- **FatigueNeuropathy less frequent than with thalidomide or bortezomib. Lenalidomide may be appropriate for patients with either disease or treatment-related neuropathy but those with pre-existing neuropathy may develop worsening symptoms.**
- **Skin rash**
- **Muscle cramps**
- **Thyroid dysfunction**
- **Diarrhoea, particularly with long-term usage**

Table 11 Guidelines for the management of bortezomib and thalidomide-induced PN evaluated according to the National Cancer Institute's Common Terminology Criteria for Adverse Events. Reproduced from Mohty, B., El-Cheikh, J., Yakoub-Agha, I., Moreau, P., Harousseau, J.L. & Mohty, M. (2010) Peripheral neuropathy and new treatments for multiple myeloma: background and practical recommendations. Haematologica, 95, 311-319. Obtained from Haematologica/the Hematology Journal website http://www.haematologica.org

Grade of neuropathy	Bortezomib	Thalidomide
Grade 1 (paraesthesiae, weakness and/or loss of reflexes without pain or loss of function)	No action	No action
Grade 1 with pain or Grade 2 (interfering with function but not with daily activities)	Reduce bortezomib to 1.0 mg/m^2	Reduce thalidomide dose to 50% or suspend thalidomide until disappearance of toxicity, then re-initiate at 50% dose
Grade 2 with pain or Grade 3 (interfering with daily activities)	Suspend bortezomib until disappearance of toxicity then re-initiate at 0.7 mg/m^2 and administer once weekly	Suspend thalidomide until disappearance of toxicity, then re-initiate at low dose if PN grade 1
Grade 4 (permanent sensory loss interfering with function):	Discontinue bortezomib	Discontinue thalidomide

Table 12. The key features with regard to renal excretion and recommended dose adjustment in renal impairment for drugs commonly used in the treatment of myeloma

	Renally excreted	Dose reduction in renal impairment	Special warnings
Melphalan	yes	yes	Dose titration with bone marrow toxicity
Cyclophosphamide	yes	yes	
Doxorubicin	no	no	
Dexamethasone	no	no	
Thalidomide	Unchanged thalidomide was <3% of the dose in urine but pharmacologically active metabolites are excreted in the urine	no	The manufacturer recommends that patients with severe renal impairment should be carefully monitored for adverse reactions
Bortezomib	no	no	
Lenalidomide	yes	yes	

APPENDIX 1: Strength of recommendation and quality of evidence

Table 1 -

STRENGTH OF RECOMMENDATIONS:

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Table 2

QUALITY OF EVIDENCE

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what we know or our certainty.

(A) High Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g. inconsistent results, imprecision - wide confidence intervals or methodological flaws - e.g. lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis),or very strong evidence from observational studies or case series (e.g. large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

(http://www.gradeworkinggroup.org/index.htm).

APPENDIX 2: recommended dose reductions for various toxicities

Bisphosphonates and renal function

Adverse effects on renal function have been reported with the nitrogen-containing bisphosphonates (pamidronate and zoledronic acid) and are most likely if the recommended dose or rate of infusion is exceeded (Barri *et al,* 2004; Berenson *et al,* 1998; Chang *et al,* 2003; Rosen *et al,* 2001). Although acute renal dysfunction may be reversible, renal impairment due to acute tubular necrosis may result in chronic renal failure. Pamidronate has also been associated with nephrotic syndrome due to a collapsing variant of focal segmental glomerulosclerosis, which can lead to end-stage renal failure. Patients with pre-existing renal impairment are thought to be particularly susceptible to bisphosphonate-induced renal damage. It is essential to check the creatinine before each infusion of pamidronate and zoledronic acid and withhold the next dose until the renal function has returned to within 10% of the baseline value.

The manufacturers' guidance on dose reduction in renal impairment is currently as follows: *Clodronate*: half dose if creatinine clearance 10–30 ml/min; contraindicated if <10 ml/min.

Pamidronate: slower infusion rate (20 mg/h) if mild to moderate renal impairment; not recommended if creatinine clearance <30 ml/min.

Zoledronic acid: Reduced dosing recommended in patients with creatinine clearance 30-60 ml/min; not recommended if serum creatinine >35 µmol/l.

Potentially this would mean that patients with severe renal failure including those on dialysis could not be treated with a bisphosphonate.

However the SPC for Pamidronate states that 'Pamidronate should not be administered to patients with severe renal impairment (creatinine clearance < 30 ml/min) unless in case of life-threatening tumour induced hypercalcaemia where the benefit outweighs the potential risk', although does not make dose recommendations in this circumstance.

In addition there is wide clinical experience of using 30mg of pamidronate in patients with severe renal impairment and appears safe if administered at a slower rate of 2-4 h. Its use should be in consultation with a renal physician. (Grade C Evidence level IV)

The following table summarizes the recommended dose reductions of bisphosphonates in renal impairment

Creatinine clearance	Sodium clodronate	Pamidronate	Zoledronate
30/35-60 ml /min	No dose modification	No dose modification. The infusion rate should not exceed 90mg over 4 h	No dose modification
10 -30 ml/min	Half dose	30 mg to be given over 2-4 h	Not recommended
< 10 ml/min	Contra indicated	30 mg to be given over 2-4 h	Not recommended

Lenalidomide and myelosuppression

Table A. Dose adjustment levels for lenalidomide

Starting daily dose	25mg
Daily dose level – 1	15mg
Daily dose level – 2	10mg
Daily dose level – 3	5mg

Table B. Dose adjustment for thrombocytopenia

When Platelets	**Action**
First fall to <30 x10^9/l	Pause lenalidomide treatment
Return to >30 x10^9/l	Resume at dose level – 1
For each subsequent drop to <30 x10^9/l	Pause lenalidomide treatment
Return to >30 x10^9/l	Resume at next lower dose level; do not dose below 5mg daily.

Table C. Dose adjustment for neutropenia

When Neutrophils	Action
First fall to < 0.5 x 10^9/l	Interrupt lenalidomide treatment
Return to ≥ 0.5 x 10^9/l when neutropenia is the only observed toxicity	Resume lenalidomide at starting dose once daily

Return to ≥ 0.5 x 10^9/l when dose-dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at dose level –1 once daily
For each subsequent drop below < 0.5 x 10^9/l	Interrupt lenalidomide treatment
Return to ≥ 0.5 x 10^9/l	Resume lenalidomide at next lower dose level (Dose level 2 or 3) once daily. Do not dose below 5 mg once daily.

Lenalidomide and renal impairment

Given the increased incidence of grades 3 and 4 thrombocytopenia in patients with impaired renal function, careful platelet monitoring is highly recommended in patients with an elevated serum creatinine, and attention is drawn to the importance of dose adjustment due to renal impairment (Table D). There are currently no recommendations for dose adjustments in patients with hepatic insufficiency.

Table D. Suggested dose reductions for renal insufficiency

Renal Function (creatinine clearance)	Dose Adjustment
Mild renal impairment (creatinine clearance ≥ 50 ml/min)	25 mg once daily (full dose)
Moderate renal impairment (30 ≤ creatinine clearance < 50 ml/min)	10 mg once daily
Severe renal impairment (creatinine clearance < 30 ml/min, not requiring dialysis)	15 mg every other day
End-stage renal disease (ESRD) (creatinine clearance < 30 ml/min, requiring dialysis)	5 mg once daily (following dialysis on dialysis days)

APPENDIX 3 : Evidence summaries

Table 1: Results of trials comparing thalidomide-based induction with conventional chemotherapy

Treatment regimens (n)	**Response rate >PR (%)**	**CR (%)**	**Reference**
TD (103) vs dex (104)	63 vs 41 (p=0.0017)	4 vs 0	Rajkumar *et al,* 2006
TD (235) vs dex (235)	63 vs 46 (P <0.001)	7.7 vs 2.6 p=0.02	Rajkumar *et al,* 2008
TAD vs VAD (402)*	72% *vs.* 54% (*p*<0.001)	7 vs 3	Lokhorst *et al,* 2010
TD vs VAD (204)*	NA	24.7 vs 7.3# (p=0.0027)	Macro *et al,* 2006
T-VAD- doxil (117) vs VAD-doxil (115)	81.2 vs 62.6 (p=0.003)	15.4 vs 12.2	(Zervas *et al,* 2007)
CTD vs C-VAD (1114)*	87.1 vs 74.8	19.4 vs 9.4	Morgan *et al,* 2009

those where induction therapy was followed by planned SCT are marked *.

only VGPR reported

TD, thalidomide plus dexamethasone (dex); TAD, thalidomide, doxorubicin, dexamethasone; VAD, vincristine, doxorubicin, dexamethasone; T-VAD, VAD plus thalidomide; C-VAD, VAD plus cyclophosphamide; CTD, cyclophosphamide, thalidomide and dexamethasone.

Table 2: Results of phase II/III studies of bortezomib /dexamethasone induction therapy

	n	RR (%)	CR (%)	Number proceeding to SCT	References
Bortezomib/ bortezomib-dex (added if <PR after 2 cycles)	32	88	6	8	Jagannath *et al,* 2005b
Bortezomib and dexamethasone	52	66	21	42 (88%)	Harousseau *et al,* 2006
Bortezomib alternating	40	65	12.5	37	Rosiñol *et*

with dexamethasone					*al,* 2007
PAD	21	95	24	18 (18/21)	Oakervee *et al,* 2005
Bortezomib- Doxil-dex	30	89	32**	17/30	Jakubowiak *et al,* 2006
VCD	300	84	10	NA	Einsele *et al,* 2009
CyBORD	33	88	39**	23/33	Reeder *et al,* 2009
Bortezomib and dexamethasone vs VAD	482	78.5 vs 62.8 (p=0.0003)	5.8% vs 1.4% (p=0.012)		Harousseau *et al,* in press
PAD vs VAD	300	85 vs 59	5 vs 1	NA	Sonneveld *et al,* 2008
TD vs VTD vs VMCP/VBAP/bortezomib	290	64 vs 82 vs 75	14 vs 29 vs 25	177	Rosiñol *et al,* 2009

** only CR/nCR reported

dex, dexamethasone; PAD, ; VCD, bortezomib (Velcade) cyclophosphamide and dexamethasone; CyBORD, cyclophosphamide, bortezomib, dexamethasone; VAD, vincristine, doxorubicin, dexamethasone; TD, thalidomide plus dexamethasone; TAD, thalidomide, doxorubicin, dexamethasone; VMCP, vincristine, melphalan, cyclophosphamide, prednisone; VBAP, vincristine, carmustine, doxorubicin, prednisone.

Table 3: Results of phase II studies of lenalidomide and dexamethasone +/- as induction therapy

	Patients	Response rate (%)	CR rate (%)	Reference
Lenalidomide/ dexamethasone	34	91	6	Rajkumar *et al,* 2005
Clarithromycin (Biaxin), lenalidomide and dexamethasone (BiRD)	72	90.3	38.9	Niesvizky *et al,* 2008
Lenalidomide/ cyclophosphamide/	53	83	2	Kumar *et al,* 2008c

dexamethasone				
Lenalidomide and high dose vs low dose dexamethasone	445	76 *	16*	Rajkumar *et al,* 2010

* after 4 cycles of treatment (90 of these patients proceeded to stem cell transplant)

Table 4: Results of trials investigating combinations involving 2 or more novel agents as induction therapy prior to SCT

		RR	CR	Type of trial	reference
TD vs VTD vs VBMCP/VBAP alternating with Velcade	290	64 vs 82 vs 75	14 vs 29 vs 25	Phase III	Rosiñol *et al,* 2009
VTD vs TD	474	92 vs 78.5% P<0.001	19 vs 5% P<0.001	Phase III	Cavo *et al,* 2009
RVD	66	98	36 CR + nCR	phase I/II	Richardson *et al,* 2009
VDCR	33	94	15	Randomized phase I/II	Kumar *et al,* 2009b

TD, thalidomide plus dexamethasone; VTD, bortezomib (Velcade) thalidomide and dexamethasone; VBMCP, vincristine, BCNU (carmustine) melphalan, cyclophosphamide, prednisone; VBAP, vincristine, carmustine, doxorubicin, prednisone; RVD, lenalidomide, bortezomib, dexamethasone; VDCR, cyclophosphamide, bortezomib, dexamethasone, lenalidomide.

Table 5: Summary of randomized trials comparing MPT with MP as induction therapy in elderly patients

Study	*Regimen*	n	CR (%)	>PR(%)	Median PFS (months)	*Median OS (months)*
IFM 99-06 (Facon *et al,*	MPT vs MP vs	125 196	13 2	76 35	27.5 17.8	51.6 33.2

2007)	MEL100*	126	18	65	19.4	38.3
IFM 01-01 (Hulin 20097)	MPT vs MP	113 116	7 1	61 31	24.1 19	45.3 27.7
(Gulbrandsen *et al,* 2008)	MPT vs MP	357 evaluable	6 3**	42 28	16 14	29 33
HOVON 49 study (Wijermans *et al,* 2008)	MPT vs MP	165 168	2 2	66 47	13 9	37 30
GIMEMA (Palumbo *et al,* 2006), updated in (Palumbo *et al,* 2008a)	MPT vs MP	129 126	15.5 2	76 48	21.8 14.5	45.0 47.6

* This study involved a 3-way randomization, including an arm consisting of standard induction followed by intermediate dose melphalan and stem cell rescue.

** CR/nCR only reported

(n)CR, (near) complete response; PR, partial response; MPT, melphalan, prednisolone, thalidomide; MP, melphalan, prednisolone; MEL100, melphalan 100 mg/m^2.

Table 6: Summary of randomized controlled trials comparing conventional chemotherapy with high dose therapy and ASCT

Trial	n	EFS (median, months)	OS (median, months)	Reference
IFM90 Conventional SCT	100 100	8% @ 7 years 16% @7 years	25% @ 7 years 43% @ 7 years	Attal *et al,* 1996; Harousseau *et al,* 2005
MRC Myeloma VII Conventional SCT	200 201	32 54 months	20 42	Child *et al,* 2003
MAG91				

Conventional SCT	91 94	13 39	64 65	Fermand *et al,* 1998
PETHEMA Conventional SCT	 83 81	 34 43	 67 67	 Blade *et al,* 2001

EFS, event-free survival; OS, overall survival; SCT stem cell transplantation.

Table 7: Results of prospective, 'biologically randomized' studies of tandem autografting compared to ASCT/ RIC Allo (adapted from San-Miguel, J.F. & Mateos, M.V. (2009) How to treat a newly diagnosed young patient with multiple myeloma. Hematology 2009: American Society of Hematology Education Program Program Book, 555-65., with permission. © the American Society of Hematology)

Cooperative group	Patients (n)	CR (%)	EFS (months)	OS (months)	P value
IFM (Garban *et al,* 2006)*	166 vs 46	37 vs 55	25 vs 21	57 vs 41	NS
GIMEMA (Bruno *et al,* 2007)	82 vs 80	26 vs 55	33 vs 37	64 vs NYR	S (both)
PETHEMA (Rosiñol *et al,* 2008)**	82 vs 25	11 vs 40	20 vs 26	58 vs 60	NS
HOVON (Lokhorst *et al,* 2008)#	101 vs 115	42 vs 45	34 vs 39	63 vs 56	NS
EBMT (Bjorkstrand *et al,* 2009)	250 vs 110	41 vs 52	15 vs 36	50 vs 65	

*patients with poor-risk disease as defined by the presence of deletion 13q by FISH along with elevated B2-microglobulin (> 3 mg/L)

**patients failing to achieve at least near complete remission (nCR) after first ASCT

patients underwent biological randomization to receive either RIC-allo after first ASCT or maintenance therapy

S = significant p value

NS = non-significant p value

IFM, Intergroupe Francophone du Myélome; GIMEMA, Gruppo Italiano Malattie Ematologiche dell'Adulto; PETHEMA, Programa para el Estudio y Tratamiento de las Hemopatias Maligna; HOVON, Stichting Hemato-Oncologie voor Volwassenen Nederland; EBMT, European Group for Blood and Marrow Transplantation.

Table 8: Summary of selected reported series of Allo-SCT in MM.

FI AlloSCT						
Conditioning Regimen	**n**	**CR %**	**TRM %**	**EFS (%)**	**OS (%)**	**Ref**
Cyclophosphamide/TBI	39	47.2	31.5	13.3 (5 years)	28.1 (5 years)	Hunter et al, 2005
Melphalan/TBI	78	54.7	35.3	36.2 (5 years)	44.1 (5 years)	Hunter et al, 2005
Bu/Cyclo/TBI	15	53.3	17	31 (6 years)	77 (6 years)	Kroger et al, 2003
Cyclo/TBI (+/-Idarubicin)	53	19	34	median 18 months	median 25 months	Lokhorst et al, 2003
Cyclo/TBI			53	22 (7 years)	39 (7 years)	Barlogie et al, 2006a
Mel/TBI	72	38	22	31.4 (10 years)	39.9 (10 years)	Kuruvilla et al, 2007
RIC AlloSCT						
Conditioning Regimen	**n**	**CR**	**TRM**	**EFS (%)**	**OS (%)**	**Ref**
Flu/Bu/ATG	41	24	17	41 (2 years)	62 (2 years)	Mohty et al, 2004
Flu/TBI_{200Gy}	52	27	17	29.4 (1.5 years)	41 (1.5 years)	Gerull et al, 2005
ASCT→Flu/TBI_{200Gy}	16	62	16	36 (3 years)	62 (3 years)	Bruno et al, 2007
ASCT→Flu/Bu	46	33	11	-	57 (2 years)	Garhton et al, 2001
ASCT→Flu/Mel/ATG	17	73	18	56 (2 years)	74 (2 years)	Kroger et al, 2002
ASCT→TBI_{200Gy}	54	57	7	45 (4 years)	69 (4 years)	Maloney et al, 2003
ASCT→ Flu/Bu/ATG	65	62.2	10.9	median 32 months	median 35 months	Garban et al, 2006
ASCT→Flu/Mel/TBI_{200Gy}	45	64	36	13 (3 years)	36 (3 years)	Lee et al, 2003b
[Non-relapse/Ref]	12	-	-	80 (3 years)	80 (3 years)	

Key: FI – full intensity/myeloablative conditioning, RIC – reduced intensity conditioning, TRM – treatment-related mortality, ASCT→: Planned tandem autologous stem cell transplantation followed by an allogeneic stem cell transplantation; Flu: Fludarabine; TBI_{200Gy}: single fraction total body irradiation; Bu: intravenous busulphan; Cyclo, cyclophosphamide; ATG: anti-thymocyte globulin; Mel: high dose Melphalan

Table 9: Results of randomized prospective studies investigating thalidomide as potential maintenance therapy post autologous transplantation

Study/Reference	Patient	PFS	OS	Duration and dose

	Numbers			
IFM 99-02 (Attal *et al,* 2006)	597	3-year 52% versus 37% (p=0.002)	4-year 87% versus 77% (P=0.04)	Median 15 months, 200 mg per day
Total Therapy (Barlogie *et al,* 2006b)	668	5-year 56% versus 41% (p=0.01)	No benefit	Until relapse or toxicity, 400 mg per day
Thalidomide and prednisolone (Spencer *et al,* 2009)	269	3-year 42% versus 23% (p<0.001)	86% versus 75% (p=0.004)	12 months, 200 mg per day

APPENDIX 4 : Suggested proforma for the early detection of bortezomib-associated toxicities.

BORTEZOMIB NURSING ASSESSMENT											
NAME:				**HOSPITAL NUMBER:**						**WT**:	
CYCLE:	**DATE:** **DAY/WEEK:**			**Hb**:		**PLTS**:				**NEUTS**:	
Temp		**Pulse**		**BP**		**RR**		**Sats**		**AVPU**	
NEUROPATHY SCORE											
0		**1**		**2**		**3**		**4**			
None		Mild tingling not interfering with function **INFORM DR**		Numbness, cramps, burning sensation or stabbing pain. Not interfering with activities of daily living (ADL) **INFORM DR**		Numbness, burning or pain, Interfering with ADL **INFORM DR**		Severe pain and permanent loss of function **INFORM DR**			
ABDOMINAL PAIN											
None		Mild pain not interfering with function		Moderate pain; pain or analgesics interfering with function but not with ADL **INFORM DR**		Severe pain; pain or analgesics severely interfering with ADL **INFORM DR**		Life threatening consequences **INFORM DR**			
NAUSEA/VOMITING											
None		1 episode in 24 hours		2-5 episodes in 24 hours may require IV Fluids **INFORM DR**		>5 episodes in 24 hrs requiring IV Fluids **INFORM DR**		Life threatening consequences **INFORM DR**			
DIARRHOEA											
None		1-3 episodes in 24 hours, advise to increase fluid intake **INFORM DR**		4-6 episodes in 24 hours may require IV fluids: not interfering with ADL **INFORM DR**		>6 episodes in 24 hours: requiring IV fluids: interfering with ADL **INFORM DR**		Life threatening consequences **INFORM DR**			
CONSTIPATION											
None		Occasional or intermittent symptoms; occasional use of laxatives		Persistent symptoms with regular use of laxatives **INFORM DR**		Symptoms interfering with ADL; enema required **INFORM DR**		Life threatening consequences **INFORM DR**			
FATIGUE											
None		Mild fatigue, Over baseline/ little tired		Moderate or causing difficulty to ADL **INFORM DR**		Severe fatigue, interfering with ALL ADL's **INFORM DR**		Debilitating **INFORM DR**			
AUTONOMIC NEUROPATHY											
None		Occasional dizziness on standing (<x3 per week) **INFORM DR**		Regular dizziness on standing with no postural drop (>3 x per week) **INFORM DR**		Postural drop >20mmHg +/- regular Dizziness **INFORM DR**		> 1 syncopal episode (fainting) associated with fall in BP **INFORM DR**			
DAY 1 ONLY		**Lying BP**				**Standing BP**					
CANNULA GAUGE:				**VEIN USED:**						**BY:**	
DOSE REDUCED DATE:				**NEUROPATHY QUESTIONNAIRE D1 & 8:**							

OTHER SIDE-EFFECTS/EVALUATION:

NAME……..
SIGNATURE:……...