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Guidelines for supportive care in multiple myeloma 2011

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Summary

Supportive care plays an increasingly important role in the modern management of multiple myeloma. While modern treatments have significantly prolonged overall and progression free survival through improved disease control, the vast majority of patients remain incurable, and live with the burden of the disease itself and the cumulative side effects of treatments. Maintenance of quality of life presents challenges at all stages of the disease from diagnosis through the multiple phases of active treatment to the end of life. Written on behalf of the British Committee for Standards in Haematology (BCSH) and the UK Myeloma Forum (UKMF), these evidence based guidelines summarize the current national consensus for supportive and symptomatic care in multiple myeloma in the following areas; pain management, peripheral neuropathy, skeletal complications, infection, anaemia, haemostasis and thrombosis, sedation, fatigue, nausea, vomiting, anorexia, constipation, diarrhoea, mucositis, bisphosphonate-induced osteonecrosis of the jaw, complementary therapies, holistic needs assessment and end of life care. Although most aspects of supportive care can be supervised by haematology teams primarily responsible for patients with multiple myeloma, multidisciplinary collaboration involving specialists in palliative medicine, pain management, radiotherapy and surgical specialities is essential, and guidance is provided for appropriate interdisciplinary referral. These guidelines should be read in conjunction with the BCSH/UKMF Guidelines for the Diagnosis and Management of Multiple Myeloma 2011.

Keywords: myeloma, supportive care, pain, peripheral neuropathy, anaemia, thromboembolism.

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1. Introduction: definitions and methodology

In the vast majority of patients, myeloma is an incurable disease. In recent years, an evolving array of effective treatments have increased the ability to achieve disease control repeatedly to the extent that myeloma now has the potential to be a chronic disease in many patients. The improvement in survival is reflected by the UK Medical Research Council (MRC) myeloma trials and other epidemiological data, and for example, with modern management younger patients responding to intensive treatment can now expect to survive for a median of approximately 7 years from diagnosis (Morgan *et al*, 2009) or potentially longer (Brenner *et al*, 2008, 2009). However, the improved survival of patients with myeloma has resulted in an increasing symptom burden due not only to the disease itself, but to also the cumulative effects of treatments. The major challenge of modern myeloma management is therefore matching the progress made in prolonging survival through disease control whilst optimizing global quality of life with effective supportive care measures from initial diagnosis to end of life care.

The aim of these guidelines is to summarize a national consensus of the haematological community and colleagues involved in the supportive care of patients with myeloma. For the purpose of these guidelines, the definition adopted in the UK National Health Service (NHS) National Institute for Health and Clinical Excellence (NICE) Guidance (NICE, 2004) has been used i.e. 'care that helps the patient and their family to cope with cancer and treatment of it – from pre-diagnosis and treatment, to cure, continuing illness or death and into bereavement. It helps the patient to maximize the benefits of treatment and to live as well as possible with the effects of the disease. It is given equal priority alongside diagnosis and treatment'. This definition is sufficiently broad to cover not only to cover symptomatic treatment and palliative care but also the wide range of management options considered to be 'haematological supportive care', including anti-infectives, transfusion therapy, anticoagulation and growth factors.

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Although much of the supportive care can be provided by the haematologists and their teams principally responsible for the care of patients with myeloma, if patients fail to respond or experience intolerable side-effects, advice should be sought from other specialist teams. In some patients, satisfactory symptomatic management is often only achieved through good multidisciplinary collaboration and specialist input from colleagues in Palliative Medicine, Pain Management, Clinical Oncology and Orthopaedics. This is probably best achieved through the routine multidisciplinary team (MDT) meetings (NICE, 2003a). Management of psychological aspects is also important. Outside of the hospital environment referral can be made to the community palliative care team or local hospice service.

These guidelines should be read in conjunction with the British Committee for Standards in Haematology (BCSH) Guidelines for Diagnosis and Management of Multiple Myeloma 2011 (Bird *et al*, 2011), which they complement. Management of symptoms in patients with myeloma at all stages should follow the principles of evidence-based palliative medicine, where possible. Where appropriate, levels of evidence are provided. As there was a view that many haematologists would welcome specific guidance in certain areas, certain therapeutic regimens have been suggested, most of which would be in the remit of haematological practice. In other areas, the guidelines make suggestions for specialist care outside of haematology. However, these guidelines should not be taken as prescriptive as variations exist. The guidance may not be appropriate to all patients and individual patient circumstances or clinician preferences may reasonably favour an alternative approach.

The draft guideline was produced by the writing group consisting of authors, assisted by other members of the broader BCSH Myeloma Guidelines group. Involvement of patient advocacy was achieved through Myeloma UK. The guidelines were subsequently revised by consensus by the UK Myeloma Forum Executive and members of the Haemato-Oncology Task Force of the BCSH. The guidelines were then reviewed by a sounding board of approximately 100 UK haematologists, the BCSH the British Society for Haematology Committee and the comments incorporated where appropriate. Criteria used to quote levels and grades of evidence where specified are as outlined in appendix 3 of the Procedure for Guidelines Commissioned by the BCSH (http://www.bcshguidelines.com/BCSH_PROCESS/42_EVIDENCE_LEVELS_AND_GRADES_OF_RECOMMENDATION.html) and US Agency for Healthcare Research and Quality (summarized in the Appendix I). 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.

The use of these guidelines to assist management of individual patients should be combined with appropriate professional training. All drug doses should be checked at reference sources, such as the British National Formulary (BNF), Palliative Care Formulary (PCF) or similar. The authors, BCSH or publishers cannot take legal responsibility for individual patient management.

2. Management of anaemia

Anaemia (haemoglobin concentration <120 g/l) is common in myeloma and is present in approximately 75% of patients at diagnosis (Kyle *et al*, 2003). In most patients the anaemia will be normochromic and normocytic and attributed to the myeloma itself and/or the myelosuppressive effect of the chemotherapy. Other causes, such as haematinic deficiency or bleeding, should be excluded. Fatigue is also reported by many patients and may be caused by both physical and psychological factors related to the disease and its treatment but anaemia has been shown to be an important contributory factor (Cella *et al*, 2004). A European wide survey in patients with myeloma suggested that prevalence of anaemia during chemotherapy is around 85% (Birgegard *et al*, 2006).

Anaemia may be managed by blood transfusion or treatment with erythropoiesis-stimulating agents (ESAs). Blood transfusion may be very helpful in the short-term correction of moderate to severe anaemia in a symptomatic individual. Minimally or asymptomatic individuals with mild or moderate anaemia (due to their disease) may be observed and some will become less anaemic as the myeloma is controlled with chemotherapy. ESA treatment is recommended for anaemic patients with myeloma with associated renal impairment (Locatelli *et al*, 2004). ESA doses of <20 000 iu/week may be adequate in patients where renal disease is the main cause of the anaemia. In the UK, it may be necessary to refer the patient to a renal physician to access NHS funding for ESAs.

Data from randomized trials, which have included patients with myeloma, suggest that ESAs increase the haemoglobin concentration in around two thirds of patients, reduce transfusion need and have a significant positive impact on quality of life (Littlewood *et al*, 2001; Osterborg *et al*, 2002; Hedenus *et al*, 2003).

Recent guidelines from the American Society of Haematology and American Society of Clinical Oncology recommend ESAs to be administered at the lowest dose possible and should increase the haemoglobin to the lowest concentration possible to avoid transfusions (Rizzo *et al*, 2010). European guidelines suggest consideration is given to initiating ESAs in symptomatic patients with a Hb of <110 g/l (Bokemeyer *et al*, 2007). In the UK, NICE has not recommended treatment for cancer-treatment related anaemia (except in ovarian cancer).

In patients undergoing high dose therapy, treatment with ESAs during the period of cytopenia has no impact on reducing transfusion need. In contrast, some studies with small numbers of patients suggest that starting ESA treatment on day +30 can increase haemoglobin concentration and reduce transfusion need after both autologous and allogeneic transplants (Baron *et al*, 2003; Vanstraelen *et al*, 2005).

There is an increased risk of thrombotic events in patients with cancer who are treated with ESAs (relative risk 1·67). Concerns about an increased mortality in ESA-treated patients have also been raised but there are no data suggesting that the outcome of patients with myeloma is worse after ESA treatment. In patients with cancer being treated with chemotherapy there is no difference in survival in randomized trials between those receiving an ESA and those treated by placebo (relative risk 1·04) (Bohlius *et al*, 2009).

Myeloma patients being treated with thalidomide or lenalidomide have an increased risk of thrombotic events. There are conflicting reports about whether this risk is further enhanced by treatment with ESA (Bennett *et al*, 2006; Menon *et al*, 2008).

Recommendations

- **A therapeutic trial of ESA should be considered in a patient with persistent symptomatic anaemia (typically haemoglobin concentration <100 g/l) in whom haematinic deficiency has been excluded (Grade A recommendation; level 1b evidence)**
- **One of Darbepoetin (6·25 μg/kg every 3 weeks), Epoetin alfa (40 000 iu once weekly or Epoetin Beta (30 000 iu once weekly) sub-cutaneously can be chosen. Dose doubling after 4 weeks in patients with a haemoglobin increase of <10 g/l can be considered (Grade B recommendation; level 2a evidence). ESA treatment should be stopped after 6–8 weeks if there has been no haemoglobin response. The haemoglobin concentration should not rise above 120 g/l (Grade C recommendation; level IV evidence).**
- **Patients with anaemia attributed to renal failure should have a trial of treatment with ESA (Grade B recommendation; level IIa evidence)**
- **True or functional iron deficiency occurring during treatment with an ESA should be treated with intravenous iron (National Comprehensive Cancer Network (NCCN), 2010).**

3. Haemostasis and thrombosis issues

3.1 Bleeding risks

Bleeding is rarely associated with myeloma at presentation, more commonly resulting from disease progression, thrombocytopenia (immune-mediated or due to marrow infiltration), renal failure, infection and therapy toxicity. Paraproteinaemia in myeloma has, however, been reported to cause bleeding due to acquired von Willebrand disease (VWD) (Sampson *et al*, 1983), platelet dysfunction (Di Minno *et al*, 1986), fibrin polymerization defects (Coleman *et al*, 1972), hyperfibrinolysis (Sane *et al*, 1989) or circulating heparin-like anticoagulants (Llamas *et al*, 2001) and, in AL amyloidosis, factor X deficiency (Mumford *et al*, 2000). Generally, a reduction in plasma paraprotein (by plasmaphaeresis and/or cytoreductive therapy) will improve haemorrhagic manifestations due to, or exacerbated by, paraproteinaemia. Prothrombin complex concentrates, recombinant factor VIIa and splenectomy have been reported to be successful in the management of some bleeding episodes in patients with factor X deficiency due to AL amyloidosis (Boggio & Green, 2001; Thompson *et al*, 2010). There is no consensus on the management of acquired VWD in myeloma. Bleeding episodes have been managed with variable success with desmopressin (transient if any response), intravenous immunoglobulin infusions (usually result in both clinical and laboratory improvement), factor VIII/von Willebrand factor concentrates (variable clinical and laboratory responses) (Federici, 2006). Management of bleeding in myeloma patients will need to be individualized and no general recommendation can be made.

3.2 Thrombotic risks

Myeloma and other plasma cell disorders have a well-established association with venous thromboembolism (VTE) (Srkalovic *et al*, 2004). A recent retrospective study of US Veterans Affairs hospital records found the incidence of deep vein thrombosis (DVT) to be 8·7/1000 in patients with myeloma, in comparison to patients with monoclonal gammopathy of undetermined significance (MGUS; 3·1/1000) or those without plasma cell disorders (0·9/1000) (Kristinsson *et al*, 2008). 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. The risk of VTE with lenalidomide alone appears to be lower than with thalidomide. Neither drug used as monotherapy significantly increases risk, but when combined with high-dose steroids or cytotoxic agents the risk of VTE increases significantly (Richardson *et al*, 2006a; Dimopoulos *et al*, 2007; Weber *et al*, 2007). The risk of VTE appears to be higher in patients with newly diagnosed myeloma treated with lenalidomide and dexamethasone (25–75%) (Zonder *et al*, 2006; Rajkumar *et al*, 2009).

3.2.1 Assessment of risk of VTE. As recommended for all patients when admitted to hospital, those with myeloma should be assessed for their risk of developing a VTE, and appropriate chemical thromboprophylaxis [low molecular weight heparin (LMWH) or fondaparinux] given.

All myeloma patients starting thalidomide or lenalidomide should undergo a risk assessment for VTE (see Table I). The reported rates of VTE associated with thalidomide and lenalidomide vary considerably depending on whether the patient is newly diagnosed or relapsed/refractory, and are influenced by the concomitant use of ESAs. This assessment needs to take into consideration patient factors (e.g. previous VTE, obesity, co-morbidities), myeloma-related factors (e.g.

Table I. Risk assessment model for the prevention of venous thromboembolism in multiple myeloma patients treated with thalidomide or lenalidomide [adapted, with permission, from Palumbo *et al* (2008a)]. © 2008 Nature Publishing Group.

Individual/Myeloma risk factors	
New diagnosis Myeloma	
Hyperviscosity	
Personal or family history of VTE	If no risk factors (RF) or only 1 RF consider aspirin
Obesity (Body Mass Index ≥ 30)	If 2 or more RF present consider either:
Co-morbidities: cardiac, diabetes, renal impairment, chronic inflammatory disease	LMWH (high risk prophylactic dose e.g. enoxaparin 40 mg od) or Warfarin (target INR 2·5)
Immobility (acute or chronic)	
Thrombophilias, myeloproliferative disorders, haemoglobinopathies	
Recent surgery (within 6 weeks): neuro-, trauma, orthopaedic, general, other	
Medications: erythropoiesis stimulating agents, hormone replacement therapy, tamoxifen/stilboestrol	
Myeloma therapy	
Doxorubicin	LMWH (high risk prophylactic dose e.g. enoxaparin 40 mg od) or Warfarin (target INR 2·5)
High-dose steroid (≥480 mg/month dexamethasone or equivalent)	
Combination chemotherapy	
Bleeding risk factors: the presence of a bleeding risk factor should prompt clinicians to consider whether bleeding risk is sufficient to preclude pharmacological thromboprophylaxis.	
Active bleeding	
Haemophilia or other known bleeding disorder	
Platelet count $<100 \times 10^9$/l	
Acute stroke in previous month (haemorrhagic or ischaemic)	
Blood pressure >200 mmHg systolic or >120 mmHg diastolic	
Severe liver disease (abnormal PT or known varices)	
Severe renal disease (Creatinine clearance <30 ml/min)	
Undergoing procedure or intervention with high bleeding risk	

disease burden, hyperviscosity) and treatment-related factors (e.g. concurrent use of high-dose steroids). Patients taking hormone replacement therapy should be encouraged to discontinue it where possible.

Other patients who are not receiving thalidomide or lenalidomide may also be at risk of VTE and thromboprophylaxis may be appropriate. This is particularly true of those admitted for management of acute episodes (infection, dehydration, pain management), where their risk of thrombosis may increase dramatically. These patients' need for pharmacological thromboprophylaxis should be considered on a case-by-case basis.

3.2.2 Selection of thromboprophylactic approach. The role of LMWH in preventing VTE in medical and surgical patients is well recognized, although the efficacy of aspirin remains uncertain, and low dose warfarin has generally been shown to be ineffective (Geerts *et al*, 2004). In myeloma, the evidence base is limited and recommendations combine both broader principles and, where available, specific data.

In myeloma, a number of different thromboprophylactic strategies have been utilized in patients receiving thalidomide or lenalidomide; aspirin, LMWH or warfarin [fixed low dose or adjusted dose to achieve an International Normalized Ratio (INR) of 2·0–3·0]. Both aspirin and LMWH have been reported to reduce the incidence of VTE in patients receiving combination therapies containing thalidomide or lenalidomide. (Zonder *et al*, 2006) found that the incidence of symptomatic VTE with lenalidomide and dexamethasone fell from 75% to 15% with the introduction of aspirin 325 mg daily. (Baz *et al*, 2005) also reported a fall in the incidence of symptomatic VTE (from 58% to 18%) with the introduction of aspirin 81 mg daily in patients receiving thalidomide with combination chemotherapy. (Palumbo *et al*, 2006) found that 17% of patients receiving MPT (melphalan, prednisone, thalidomide) developed symptomatic VTE, but with the introduction of enoxaparin thromboprophylaxis, the incidence of symptomatic VTE fell to 3%. (Zangari *et al*, 2004) also demonstrated a fall in the incidence of VTE with the addition of prophylactic LMWH in patients receiving combination chemotherapy in addition to thalidomide. In this study, fixed low dose warfarin did not reduce the risk of symptomatic VTE. Adjusted dose warfarin (INR 2·0–3·0) or therapeutic dose LMWH have also been used in a small study of 26 patients

receiving primary induction with thalidomide and dexamethasone with a VTE rate of 8% (Wang *et al*, 2005). There is no evidence of benefit with fixed low-dose warfarin or using a target INR < 2.

As yet, no prospective randomized study comparing thromboprophylaxis strategies in patients receiving thalidomide or lenalidomide-containing treatment regimens has been completed. Despite the lack of clear evidence in this area, the International Myeloma Working Group recently published some recommendations regarding VTE prophylaxis in patients treated with thalidomide or lenalidomide, incorporating both patient-related and treatment-related risk factors for VTE (Palumbo *et al*, 2008a).

Risk factors are categorized into:

1 The diagnosis of myeloma itself (as a cancer) and hyperviscosity.
2 Individual, including previous VTE or inherited thrombophilia, body mass index > 30 kg/m^2, central venous catheter *in situ*, comorbidities (cardiac disease, chronic renal disease, diabetes, acute infection and immobilisation), surgery, anaesthesia and trauma and ESA administration.
3 The choice of myeloma therapy, specifically high dose dexamethasone ≥480 mg/month, doxorubicin and multiagent chemotherapy.

Incorporating co-morbidities, the majority of patients undergoing treatment for myeloma with thalidomide or lenalidomide will therefore have ≥2 risk factors, including all those receiving high dose dexamethasone or multiagent chemotherapy and, based on this approach, the recommendation is for LMWH (equivalent of enoxaparin 40 mg od or dalteparin 5000 units od) or adjusted dose warfarin (INR 2·0–3·0). Prophylactic aspirin 75–325 mg once daily should only be used in patients with ≤1 risk factor. There appears to be no benefit of thromoboprophylaxis in the relatively rare situation of patients on thalidomide or lenalidomide monotherapy.

Despite these recommendations, the risks of VTE always need to be individually balanced against the risks of bleeding (e.g. in settings where thrombocytopenia may develop or congenital or acquired haemostatic disorders) and other complications (e.g. osteoporosis). Moreover, safe and optimal administration and monitoring of LMWH and warfarin in a predominantly elderly population may present challenges. Until the results of studies comparing the efficacy of aspirin to LMWH or warfarin in patients receiving such regimens, these recommendations appear sensible (Palumbo *et al*, 2008a). Those on lenalidomide with one additional risk factor may receive aspirin 75 mg once daily but there is no evidence that this is protective for a similar group on thalidomide. The latter and those with two or more additional risk factors require greater protection in the form of prophylactic-dose LMWH.

Thrombocytopenia is a frequent obstacle to safe thromboprophylaxis, related to both marrow infiltration and myeloma treatment. Patients with platelet counts $<100 \times 10^9$/l need to be monitored closely and if the platelet count falls below 50×10^9/l, thromboprophylaxis should be paused, except in very high-risk cases, which should be discussed with a haemostasis expert.

The duration of thromboprophylaxis remains contentious. Clearly the risk of VTE falls as disease burden decreases, during which time there may be alterations in treatment (e.g. reduction in high dose dexamethasone dosing schedules). The majority of VTE in myeloma patients occur within the first 6 months of treatment. Thus, for example, thromboprophylaxis may be given for at least the first 4–6 months of treatment until disease control of active myeloma is achieved with more intensive regimens, and may then be de-escalated or discontinued. However, it is important that the strategy is individualized according to the presence of risk factors in each patient.

3.2.3 Treatment of VTE in myeloma patients. As with other patients with suspected VTE, objective diagnosis should be made using appropriate imaging investigations, and treatment should follow best practice guidelines, such as those of the American College of Chest Physicians (Kearon *et al*, 2008). No clear guidance can be given for the duration of anticoagulation in myeloma patients developing VTE, but ongoing risk assessment is reasonable. There is good evidence that, in cancer patients, where the risk of VTE recurrence after discontinuation of anticoagulation is as high as 10%, long term maintenance with LMWH is significantly less frequently associated with recurrent VTE than warfarin, without an increased risk of bleeding (Lee *et al*, 2003; López *et al*, 2004). Based on these studies, extended therapy with LMWH should be considered in myeloma patients, balancing these advantages against the inconvenience of daily injections, costs and long term complications. Those starting LMWH should have a baseline platelet count checked, and consideration given to checking further platelet counts every 2–4 d for the first 2 weeks of treatment, to screen for heparin-induced thrombocytopenia (HIT) (with a platelet count also at 24 h if the patient has received heparin (unfractionated or LMWH) in the previous 100 d). For patients at extremes of body weight, or with renal impairment (creatinine clearance <30 ml/min) treatment dose LMWH may need to be dose adjusted, given in divided doses and monitored with anti-Xa levels.

If patients have a confirmed VTE whilst taking thalidomide or lenalidomide, it is reasonable to transiently discontinue these drugs until a fully anticoagulated state is established. Anticoagulation should be continued for the total duration of the treatment and then a repeat VTE risk assessment performed to inform the duration of ongoing anticoagulation thereafter.

Recommendations

- **Cancer, cancer therapies, infection, previous VTE, immobility, obesity, paraplegia, ESA treatment, dehydration and renal failure are all well-recognized risk factors for VTE, particularly in hospitalized patients. As with other**

areas of thromboprophylaxis, a risk stratified approach is appropriate in patients with myeloma (Grade C recommendation; level IV evidence).

- **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 C recommendation; level IV evidence).**
- **In patients receiving thalidomide or lenalidomide, aspirin (75 – 325 mg) may be considered as VTE prophylaxis in low risk patients only (i.e. without risk factors, or only one myeloma/individual risk factor present), unless contraindicated (Grade C recommendation; level IV evidence).**
- **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 contraindicated. There is no role for fixed, low dose warfarin (Grade C recommendation; level IV evidence).**
- **The duration of thromboprophylaxis remains unclear but 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 C recommendation; level IV evidence).**
- **Treatment of confirmed VTE should follow current practice guidelines using adjusted dose warfarin or LMWH and appropriate monitoring (Grade C recommendation; level IV evidence).**

4. 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 d 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*, 2009; Morgan *et al*, 2009; Rajkumar *et al*, 2009). Patient education as well as access to 24-h specialist advice and treatment is crucial in preventing and managing infection in myeloma.

Streptococcus pneumoniae, *Haemophilus influenzae* and Gram negative bacilli are the most frequent causes of infection in myeloma patients (Savage *et al*, 1982). Prophylactic antibiotics may have a role in reducing infection rates but have the potential for leading to increased *Clostridium difficile* infection and antibiotic resistance. The role of prophylactic antibiotics in myeloma needs to be addressed in larger numbers of multiple myeloma patients and their routine use is not recommended. Prophylactic immunoglobulin replacement has been shown to have some benefit in reducing infection rates in patients in plateau phase (Chapel *et al*, 1994) but no effect has been demonstrated in newly diagnosed patients (Salmon *et al*, 1967). A reasonable regimen is a dose of intravenous immunoglobulin of 500 mg/kg administered every month for up to 6 months.

Studies in myeloma indicate suboptimal antibody responses to a variety of vaccines, which are particularly worse for polysaccharide rather than protein antigens (Robertson *et al*, 2000). The value of influenza vaccination is unclear in myeloma although there is some evidence for efficacy in solid tumour patients undergoing chemotherapy (Melcher, 2005). Granulocyte colony stimulating factor (G-CSF) may have a role in reducing treatment-associated neutropenia (Mateos *et al*, 2008a) and following autologous peripheral blood stem cell transplantation (Sung *et al*, 2007).

Recommendations

- **Vaccination against influenza, *Streptococcus pneumonia* and *Haemophilus influenzae* is recommended but efficacy is not guaranteed (Grade C recommendation; level IV evidence).**
- **Prophylactic immunoglobulin is not routinely recommended but may be useful in a small sub-set of patients with severe, recurrent bacterial infections and hypogammaglobulinaemia (Grade C recommendation; level IV evidence).**
- **Prophylactic aciclovir is recommended for patients receiving bortezomib therapy, following autologous stem cell transplantation or patients with recurrent herpetic infections (Grade C recommendation; level IV evidence).**

5. Pain management

5.1 Prevalence and impact of pain in myeloma

Pain is one of the commonest symptoms experienced by myeloma patients and indeed it may have been the reason for initial presentation, or of subsequent relapse. Up to 67% of patients report pain at diagnosis, although this may have been present for several months before (Kariyawasan *et al*, 2007). At diagnosis, pain may be due to the disease process itself (predominantly from destructive bone disease, but occasionally from plasmacytomas directly affecting neural tissues), or it may signify a co-morbidity (e.g. degenerative arthritis or osteoporosis). Later in the course of the disease, pain often arises as a side-effect of therapies, e.g. thalidomide or bortezomib neuropathy.

Bone pain is associated with significant morbidity and impact on activities of daily living, especially if the spine or

lower limbs are involved, impeding mobility. It is important to ask about these issues, as referral to occupational therapy or physiotherapy may be helpful alongside disease-directed therapy. Bone marrow examinations are usually associated with short-lived pain, but in some individuals this is sustained, perhaps because of neuroma formation in the biopsy site.

During intensive treatment, several pain syndromes have been identified (Niscola *et al*, 2006): these include deep somatic pain caused by growth factors and chemotherapy-induced oropharyngeal mucositis.

Particularly in older patients, it is important to always consider co-morbidities, such as arthritis or osteoporosis, mimicking bony malignant pain; diabetes or carpal tunnel syndrome mimicking peripheral neuropathy (PN); and post-herpetic neuralgia as a common cause of persistent pain.

Recommendation

- **All staff working with myeloma patients should be aware of the high incidence of pain and other symptoms, and be able to diagnose their cause (grade C recommendation, level IV evidence).**

5.2 Assessment of pain

It is important to make an accurate clinical assessment of pain, which starts with taking a history but may involve imaging by X-ray, bone scan, computerized tomography (CT) or magnetic resonance imaging (MRI). Patients can regularly be asked to score their pain on a 0–10 numerical scale (where 10 is the worst pain imaginable) at initial diagnosis and follow-up visits (Shi *et al*, 2009a). Patients unable to give a numerical score from 0 to 10 may find it easier to rate pain verbally on a four-point scale from 'none' to 'severe'. A numerical pain score of 5 or over is equivalent to moderate-severe pain and patients repeatedly scoring at this level should be referred to a palliative care or pain team (Serlin *et al*, 1995). Similarly, patients who do not achieve a reduction of two or greater on a 0–10 pain scale may benefit from specialist referral.

If the patient has more than one site of pain, these should all be assessed and recorded separately, as they may have different aetiologies and may require different interventions. A body chart is very helpful to record the sites of all pains, including radiation and dermatomal distribution for nerve root pain or the extent of stocking and glove distribution for PN. Both the body chart and 0–10 scales for patient recording of pain at rest, on movement and the impact of pain on other activities and sleep are all captured by the Brief Pain Inventory – Short Form (Shi *et al*, 2009a).

To diagnose the presence of neuropathic pain, the Leeds assessment of neuropathic symptoms and signs (LANSS) scale can be used (Bennett *et al*, 2007). Specialist neurological consultation and electrophysiological testing are not usually required, unless there are unexplained dermatomal distributions.

Recommendations

- **Pain should be assessed regularly in myeloma patients at all stages of the disease (Grade C recommendation; level IV evidence).**
- **Pain should be measured using a 0–10 scale; alternatively it can be measured on a verbal none-mild-moderate-severe scale (Grade B recommendation; level III evidence).**
- **Patients who repeatedly score pain as ≥ 5/10 should be referred to a palliative care or pain team (Grade C recommendation; level IV evidence)**
- **A reduction of two or greater on the 0–10 scale is clinically significant; if this is not achieved then the patient should be referred to a specialist (Grade C recommendation; level IV evidence).**
- **A body chart should be used to document sites of different pains (Grade B recommendation; level III evidence).**
- **The Brief Pain Inventory – Short Form should be the standard for full pain assessments (Grade A recommendation; level Ib evidence).**
- **The presence of neuropathic pain should be assessed using the LANSS scale (Grade A recommendation; level Ib evidence).**

5.3 Interventions

5.3.1 Introduction. In 1986 the World Health Organization (WHO) published its cancer pain programme which featured the three-step analgesic ladder that has been widely used (Ventafridda *et al*, 1985). In recent years the limitations of the simplistic WHO approach, in contrast to the advancements in pain science has been questioned (Ahmedzai & Boland, 2007). Our understanding of cancer pain mechanisms and modes of action of analgesic drugs has increased greatly in recent years and a modern evidence-based approach based on the pathophysiological cause of specific types of pain is desirable (http://www.britishpainsociety.org/book_cancer_pain.pdf) (Raphael *et al*, 2010a,b). Such an approach would incorporate, for example, the molecular mechanism of the drugs which target neuronal or synaptic transmission and awareness of the toxicities of drugs (Mantyh *et al*, 2002; Ballantyne & Mao, 2003; Holdcroft & Power, 2003). Cancer pain usually requires a combination therapy approach which can include an opioid, a calcium channel blocker, sodium channel blockers and noradrenaline reuptake inhibitors [serotonin–noradrenaline reuptake inhibitors (SNRIs) or tricyclic antidepressants] (Ossipov & Porreca, 2005). Depending on the experience of the haematologist and/or general practitioner, optimal treatment with systemic calcium and systemic sodium channel blockers may require prescription by or advice from a pain or palliative medicine specialist. Nonsteroidal anti-inflammatory drugs (NSAIDs) have limited use in myeloma because of the potentially serious renal toxicity.

In addition, modern pain management for myeloma should offer a range of non-pharmacological interventions

Table II. Key points to compare opioids for analgesia used in UK.

Opioid	Receptors	Routes	Equivalent 24-h dose (30mg oral morphine/day as reference point)	Advantages	Disadvantages	Renal failure	Hepatic failure	Other information
Morphine	MOR agonist	PO, IV, SC, Sp	30 mg PO = 15 mg SC, IV	Familiarity; Cheap; Available as normal release and modified release tablets	Sedation; Hallucinations; Nausea; Constipation; Immunosuppression	Do not use – high risk of toxic metabolites in renal failure	Caution if prothrombin time prolonged	Nausea usually resolves – CNS side-effects and constipation usually persist
Tramadol	MOR agonist; SNRI	PO, IM	150 mg PO (maximum recommended dose is 400 mg per 24 h)	Less constipation than morphine; SNRI action may help with neuropathic pain May be immune-enhancing	Risk of serotonin syndrome with other SNRIs	Caution	Caution	Efficacy highly dependent on CYP2D6 phenotype; SNRI activity blocked by 5HT3 antagonists
Codeine	MOR agonist	PO	300 mg PO (NB – this is higher than maximum daily dose of 240 mg)	Familiarity; available without prescription	Constipation; Sedation	Do not use – as for morphine	Caution – as for morphine	Pro-drug of morphine; CYP2D6 dependent; Often combined with paracetamol
Oxycodone	MOR, KOR agonist	PO, IV, SC	15 mg PO = 7·5 mg SC, IV	Reduced sedation, hallucinations *cf* morphine	Oral liquid unpleasant taste – use capsules; For parenteral use, concentrate (50 mg/ml) now available as substitute for diamorphine); Probably immune-neutral	Caution – plasma concentrations may rise	Safe	Females have greater response; CYP3A4 and CYP2D6 dependent
Fentanyl	MOR agonist	TM (buccal, sublingual, nasal), TD, IV, Sp	12 μg/h TD patch over 72 h	Reduced sedation, emesis, constipation *cf* morphine; Convenience of 3 d patch	TM applications very short-acting (1–2 h) – best reserved for incident (movement-related) pains and dressing changes, etc.; Probably immunoneutral	Safe in renal failure (Alternative for parenteral use is alfentanil)	Safe	Use rapid acting TM formulations with caution in patients with addictive tendencies; Affected by CYP3A4-acting drugs
Buprenorphine	Partial MOR, ORL1 agonist; KOR, DOR antagonist	TM (sublingual), TD, IV	20 μg/h TD patch over 7 d	Reduced respiratory depression; Convenience of patches (5–20 μg dose TD patches can last 7 d	Nausea with initiation of higher dose TD patch; TM tablet causes nausea	Safe	Safe	Ceiling dose for respiratory depression makes it safer for COPD patients; Does not reverse other MOR opioids at therapeutic doses

Table II. (Continued)

Opioid	Receptors	Routes	Equivalent 24-h dose (30mg oral morphine/day as reference point)	Advantages	Disadvantages	Renal failure	Hepatic failure	Other information
Diamorphine	MOR agonist	IV, SC	10 mg SC, IV	Familiarity; High water solubility	As for morphine	Do not use – as for morphine	Caution -as for morphine	Pro-drug of morphine; Has no advantages apart from high water solubility (but note that oxycodone concentrate now available in UK)

MOR, mu-opioid receptor; KOR, kappa-opioid receptor; DOR, delta-opioid receptor; ORL1, opioid-receptor-like receptor; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin–noradrenaline reuptake inhibitor; COPD, chronic obstructive pulmonary syndrome; CNS, central nervous system; PO, oral; IV, intravenous; SC, subcutaneous; Sp, spinal (epidural or intrathecal); TD, transdermal; TM, transmucosal (sublingual, buccal or nasal); IM, intramuscular.
Please note that this table has been compiled by one of the authors (SHA) as a guide for haematologists on how to use the common opioids available in the UK. Other opioids e.g. methadone and hydromorphone, are for specialist use by palliative medicine and pain management services. The new fast-acting transmucosal fentanyl products are also usually restricted to specialist initiation only. If in any doubt, e.g. possible interaction, renal failure, use of syringe drivers etc., and for further help in using opioids with myeloma patients, the haematologist should contact these local specialist services or pharmacy.
Note that, although there is a perception that there is no effective ceiling dose for morphine or other strong opioids, it is advised to seek specialist advice when *total daily doses* reach these levels – morphine 120 mg PO, 60 mg parenteral; oxycodone 60 mg PO, 30 mg parenteral; buprenorphine patch 50 μg/h; fentanyl patch 25 μg/h; diamorphine 40 mg parenteral. N.B. Some of the doses and routes stated here are outside the product licenses.
Main sources: Twycross and Wilcock (2008); Raphael *et al* (2010a); British National Formulary http://bnf.org/bnf/index.htm (last accessed 17 September 2010).

including bisphosphonates, radiotherapy, percutaneous vertebroplasty and balloon kyphoplasty, orthopaedic fixation of spine and long bones (Siemionow & Lieberman, 2008). The latter surgical interventions should be considered early in the course of disease in order to stabilize long bone and the vertebral spine from fracture and the consequent adverse effects on mobility and quality of life. For selected patients with lack of response or intolerable toxicity from systemic opioids, spinal delivery – preferably via an implanted intrathecal catheter – should be considered (Smith *et al*, 2005). Some patients, particularly those with high levels of anxiety, also benefit from psychological techniques such as relaxation therapy.

Recommendation

- **Pain arising in myeloma patients should be managed using a multi-modal, mechanism-based approach including evidence-based pharmacological therapies alongside non-drug methods, such as radiotherapy, bisphosphonates, and where appropriate, interventional and psychological techniques (Grade B recommendation; level III evidence).**

5.3.2 Non-opioid analgesics. Paracetamol is a useful analgesic in cancer-related pain and other chronic pains and should be prescribed at a dose of up to 1 g qid (p.o. or i.v. in patients who cannot take oral medication, e.g. because of vomiting or mucositis).

NSAIDs should be avoided apart from very short term use (e.g. 3–5 d) with acute severe pain, e.g. bone fracture. They should not be used in the presence of renal impairment, and used with extreme caution in myeloma patients in view of the risk of precipitating renal compromise.

Recommendations

- **Paracetamol can be prescribed up to 1 g qid (Grade B recommendation; level III evidence)**
- **NSAIDs should generally be avoided in myeloma. (Grade C recommendation; level IV evidence)**

5.3.3 Opioid analgesics. Table II summarizes the Key points relating to opioid analgesics used in the UK

5.3.3.1 *Mild pain (1–4 on a 0–10 scale):* For patients with mild pain (<5/10), and those who are opioid-naïve, normal release tramadol is a reasonable choice of analgesic agent. Tramadol has 1/5th the potency of oral morphine and the starting dose is 50 mg 6 hourly prn or qid. Patients who respond but need qid dosing are best placed onto the bd sustained release form. Codeine can also be used but it is a pro-drug of morphine, and 10–15% of the population is unable to convert it into active morphine, leaving them with unacceptable toxicity (Lötsch & Geisslinger, 2006).

5.3.3.2 *Moderate to severe chronic pain (>4/10):* Patients with chronic moderate (5–6/10) or severe pain (>6/10) can be started on tramadol as above, but will usually need to go onto more potent opioids rapidly if they do not respond. Oxycodone has twice the potency of morphine and is associated with less drowsiness and hallucinations. For rapid onset, the normal release preparation can be used 4–6 hourly or qid, but most patients eventually prefer the convenience of the bd sustained release forms (Mucci-LoRusso *et al*, 1998).

Patches can be used to deliver either fentanyl or buprenorphine, both of which are very potent opioids. Fentanyl causes significantly less nausea, sedation and constipation compared to morphine (Clark *et al*, 2004). When given the choice of fentanyl patches or oral morphine for chronic pain, patients prefer the patches (Ahmedzai & Brooks, 1997). Buprenorphine often initially causes nausea but this can be covered by the use of an anti-emetic such as metoclopramide and is otherwise well tolerated. Note that there are two formulations of buprenorphine patch – the low doses (5–10 mcg/h) are primarily for use in arthritis or other non-cancer patients, whereas the higher doses (35 mcg/h and greater) are more useful for cancer pain.

When using normal release oral medication, the dose can be titrated up daily by 30–50% until pain is controlled or unacceptable side effects occur. With sustained release oral medication it is advisable to wait 2–3 d between dose increments. With patches, doses should not normally be increased at <3 d intervals.

With all sustained release analgesics, it is essential to offer the patient a normal release 'rescue medication' for breakthrough pain. This is particularly important when breakthrough pain occurs quickly and predictably, e.g. on weight-bearing with disease in the spine or legs. It is important to distinguish this kind of 'incident pain' from pain arising from end of dose failure with sustained release medications, or spontaneous pains associated with neuropathy or opioid-induced hyperalgesia (Davies *et al,* 2009). Normal release oxycodone or morphine can be used, at 1/6th of the current 24-h total opioid dose. However, often the absorption of these oral drugs can be too slow for some episodes of breakthrough pain. Fentanyl has a high bioavailability via the transmucosal route, which has led to the development of fast-acting (but short-lived) fentanyl formulations. These include fentanyl lozenges; buccal tablets; or sublingual tablets (Weinstein *et al*, 2009; Lennernäs *et al*, 2010). Nasal sprays are now also available. Normally, a patient should not need to use more 2–3 of these relatively expensive fentanyl formulations per day for breakthrough pain; if more are being taken, either the background medication needs to be increased or the patient should be referred to a specialist. There is no place for pethidine in the treatment of pain in myeloma.

5.3.3.3 *Acute onset moderate-severe pain (>4/10):* For patients with sudden onset of moderate to severe pain, e.g. after long bone fracture or vertebral collapse, the subcutaneous route is recommended, e.g. with oxycodone or morphine, until the pain is controlled and then a sustained release oral preparation can be started. Opioids can be combined with other drugs, e.g. an anti-emetic in the syringe driver. There is usually no advantage of using the intravenous route, except in acute severe pain and this should be administered by a pain or palliative medicine specialist. Patient controlled analgesia (PCA) pumps are also of little value in myeloma patients, except in some cases of very severe oropharyngeal mucositis.

For non-emergency situations, there is no advantage of using injections or subcutaneous syringe drivers, except when the patient is vomiting or otherwise unable to take oral medication.

Diamorphine is a pro-drug for morphine and apart from its greater water solubility, it has no advantages over morphine or oxycodone for injections.

5.3.3.4 *Adverse effects of opioids:* With all opioids, it is important to offer the patient a laxative and to keep checking for the development of constipation. Transdermal fentanyl and buprenorphine are associated with reduced incidence of constipation (Clark *et al*, 2004; Tassinari *et al*, 2009). It is not necessary to routinely prescribe an anti-emetic with opioids, except for the first week when starting buprenorphine.

Most opioids cause dose-related sedation; however, fentanyl and oxycodone are associated with reduced sedation compared to morphine (Ahmedzai & Brooks, 1997; Clark *et al*, 2004; Reid *et al*, 2006). Patients who experience intolerable sedation due to opioids (or other drugs, e.g. thalidomide) may be considered for a trial of a psychostimulant such as methylphenidate or modafanil; this should only be prescribed by a specialist in palliative medicine. (See sections 7.5 and 7.6)

Respiratory depression is uncommon in patients treated chronically with opioids as long as dose increments are made carefully as outlined above. With the initiation of opioids, it is common to see a reduction in respiratory rate; however, this is usually balanced by changes in tidal volume so that minute ventilation initially remains steady. Care needs to be taken in patients with chronic obstructive pulmonary disorder or obstructive sleep apnoea, in whom the respiratory depression can occur even with low doses of opioids. True respiratory depression caused by opioids is diagnosed by a reduction in oxygen saturation (SaO_2 < 90%) or by arterial blood gases. If this occurs, naloxone can be given but care must be taken not to provoke a serious increase in pain. Advice on future opioid dosing should be sought from a specialist in pain or palliative medicine.

Recently, a condition known as opioid-induced hyperalgesia has been consistently identified in animal studies and has also been demonstrated to occur in human studies (Ballantyne & Mao, 2003). This condition is characterized by increasing reporting of pain in the presence of increasing opioid dosage. The pain can be localized to the original lesion but is often generalized to adjacent dermatomes. The skin in the affected area may show hyperalgesia (increased pain response on normal painful stimulus) or allodynia (pain felt even on light touch). This is thought to be caused by downstream intracellular signalling mechanisms from the

activated opioid receptor and involves the induction of nitric oxide and the opening of *N*-Methyl-D-aspartate (NMDA) channels, which are responsible for maintaining chronic and neuropathic pain (Mao *et al*, 2002; Mao, 2008). The management of this condition should be left to specialists in pain or palliative medicine; it involves reduction in the opioid dosage along with the introduction of an NMDA channel blocker, such as ketamine or methadone.

For details on currently available opioids and their usual starting doses; dose equivalents for conversions; calculation of prn dosing, see (Twycross & Wilcock, 2008).

Recommendations

- **For mild-moderate pain (<5/10), oral tramadol is a recommended (alternative is codeine) (Grade C recommendation; level IV evidence).**
- **For chronic moderate-severe pain (>4/10), oxycodone is recommended, either normal or sustained release (alternative is morphine) (Grade B recommendation; level III evidence).**
- **For patients with chronic moderate-severe pain, fentanyl or buprenorphine patches are convenient, cause fewer side-effects and are preferred by patients (Grade A recommendation; level Ib evidence).**
- **For acute severe pain (>6/10) it is reasonable to initiate subcutaneous opioid therapy to achieve quicker pain control, using oxycodone injection (morphine is alternative) (Grade C recommendation; level IV evidence).**
- **For non-oral medication, e.g. patient is vomiting, has reduced consciousness or is moribund, the subcutaneous route is recommended (Grade C recommendation; level IV evidence).**
- **Patients on opioids should be regularly screened for toxicity – the main treatable adverse effects being constipation, emesis and sedation (Grade C recommendation; level IV evidence).**
- **All patients on opioids should be prescribed laxatives (Grade A recommendation; level Ib evidence).**
- **Patients who develop drug-related sedation should be referred to a specialist for consideration of a psychostimulant (Grade B recommendation; level III evidence).**
- **Patients on opioids who experience increasing pain in spite of increasing doses and in the absence of increasing disease, should be considered as having opioid tolerance or opioid-induced hyperalgesia and should be referred to a pain or palliative medicine specialist (Grade C recommendation; level IV evidence).**

5.3.4 Special pain situations (see section 6 for neuropathic pain). With all chronic cancer-related pains and iatrogenic neuropathies, there is a good case for using a calcium-channel blocking agent, e.g. gabapentin or pregabalin. However, gabapentin is associated with a risk of bone marrow suppression and should be used with caution during stem cell transplantation procedures (there is presently no evidence regarding pregabalin). Both gabapentin and pregabalin should be used at a reduced dose in renal failure.

For procedural pain, e.g. patients with bone fractures who are unable to lie down for MRI scanning or radiotherapy, it can be helpful to refer to the local specialist palliative care or pain service, who may use drugs such as ketamine or propofol.

For patients with continuing severe (>6/10) pain or those who are unable to tolerate analgesics because of adverse effects, help should be sought from a specialist service such as the palliative care team or chronic pain team. They will advise on and supervise the use of options, such as ketamine, methadone or spinal analgesia.

Recommendation

- **All patients with chronic pain should be considered for a calcium channel blocker (gabapentin or pregabalin) and a sodium channel blocker (lidocaine, oxcarbazepine) and a SNRI (duloxetine or amitryptiline) (Grade B recommendation; level III evidence).**

5.4 Collaboration with specialist services

5.4.1 Palliative medicine and pain services. Haematology teams should readily seek to share care of pain and other symptoms with local palliative and supportive care teams and radiotherapy services. Patients at home can be seen by community or hospice-based palliative care teams. Hospital chronic pain teams should be consulted for severe pain if palliative and supportive care teams are not available. Acute pain teams may be helpful if the patient has an acute severe pain, e.g. bone fracture causing immobilization, which may respond to interventional procedures, e.g. local nerve blockade or spinal delivery of opioids and local anaesthetic. Orthopaedic surgeons or interventional radiologists are able to perform cement vertebroplasty or kyphoplasty for uncontrolled pain arising from vertebral collapse (see section 5.4.3). Psychologists can help with patients who have severe anxiety overlying pain and with other issues, e.g. phobias. Specialist nurses in haematology teams may have some training in symptom palliation but they should work and consult with palliative care specialist nurses and teams.

Warning signs indicating need to refer to local specialist service include:

1 Increasing pain in spite of following above guidelines (especially if opioid tolerance or opioid-induced hyperalgesia is suspected).
2 Intolerable adverse effects of standard treatments.
3 Additional psychological stresses or existential problems (e.g. coping with news of recurrence or facing death) which are preventing patients from adapting to or coping with symptoms.

4 Social or family circumstances that prevent the patient from adhering to the treatment regimen or being discharged from acute care.

The median dose of morphine (or equivalent median dose of other opioids) in patients with advanced cancer who are being treated by specialists in palliative medicine is approximately 120 mg/d. It is therefore recommended that if the total daily dose of opioid in a myeloma patient exceeds this median dose, this should be a trigger for the patient to be discussed with, or referred to, the local palliative care team. (This cut-off dose is equivalent to approximately 60 mg bd of oral morphine; 30 mg bd of oral oxycodone; 25 μg/h of fentanyl patch). However, it should be noted that in many centres, the palliative care team may be too small to cope with a large number of such referrals; or patients who are still having potentially 'curative' or 'life-prolonging' treatments may fall outside their remit.

It is important when referring to a specialist palliative care service for symptom control to reassure the patient that this does not mean that they are at 'the end of life', since that is often the assumption of the public. The best way of supporting patients is shared care between the haematology department and the supportive and palliative care team or pain service.

5.4.2 Radiotherapy for pain relief. Local radiotherapy is effective for pain relief for skeletal disease and may also palliate soft tissue disease. Relatively low-radiation doses are required with a correspondingly low incidence of side effects and with the potential for re-irradiation for local recurrence of symptoms if required. Published dose–response data specific to myeloma are very limited. Mill and Griffith (1980) reported on 278 radiation fields in 128 patients treated over a wide dose range. Pain relief occurred in 91% (21% complete) at a median dose of 10–15 Gy in 2–3 Gy fractions. Only 6% of sites required re-treatment and this was unrelated to initial dose. Leigh *et al* (1993) analysed 316 sites in 101 patients; 97% experienced pain relief (complete in 26%) with a mean dose of 25 Gy (range 3–60 Gy); 6% relapsed after a median interval of 16 months and were retreated. There was no correlation between dose and either response or relapse.

Myeloma is at least as radio-responsive as other types of skeletal metastases and it is reasonable to extrapolate guidance on radiotherapy dose and fractionation for pain relief in myeloma from randomized trials of localized radiotherapy for the treatment of bone metastases from a variety of primaries. A meta-analysis of 16 such trials concluded that there was no significant difference in complete or overall pain relief between single and multi-fraction regimes and no evidence of a dose-response relationship between 8 Gy single exposure and up to 40 Gy fractionated, although more frequent re-irradiation was noted in the lower dose arms (Wu *et al*, 1993).

Patients should have sufficient analgesia to cover the administration of radiotherapy, including the positioning necessary for its delivery and for the period following treatment until maximum benefit is achieved. In some cases it may be necessary to call on the services of the local pain or palliative care service to give acute analgesia, such as ketamine, to enable patients to lie on the table for treatment. Given that some but not all elements of pain in myeloma are radio-responsive an early reappraisal of symtomatic control measures is important.

Recommendations

- **Local radiotherapy is helpful for pain control; a dose of 8 Gy single fraction is recommended (Grade C recommendation; level IV evidence).**

5.4.3 Specialized spinal services.

5.4.3.1 *Introduction:* Although the management of spinal pain is often conservative, in the absence of instability/neurological compromise, orthopaedic, neurosurgical or interventional radiological advice should be sought in cases of persistent/refractory pain. Vertebroplasty and kyphoplasty are alternative options for controlling pain associated with vertebral collapse. Vertebroplasty and kyphoplasty are both vertebral body augmentation techniques of percutaneous injection of bone cement to the vertebral bodies. They are best performed soon after the vertebra collapses and may be ineffective if many months have elapsed. Both techniques carry the small risk of cement leakage leading to pulmonary embolism and neural compromise. It is therefore important that there is access to a spinal surgery service when these procedures are performed.

5.4.3.2 *Vertebroplasty:* This involves the percutaneous injection, under general anaesthetic and i.v. sedation and using radiological imaging, of polymethacrylate bone cement or equivalent biomaterial into the vertebral body (Jensen & Kallmes, 2002). Several vertebrae can be treated simultaneously. The injection allows local pain relief and bone strengthening but will not restore vertebral height. No randomized studies on the use of vertebroplasty in myeloma have been published. However, a recent review of 67 cases demonstrated improvements in pain (89%), mobility (70%) and use of opioid analgesia (65%) (McDonald *et al*, 2008).

5.4.3.3 *Kyphoplasty:* This involves the percutaneous insertion of a small, inflatable balloon into the vertebral body; when inflated it produces a potential space. The balloon is then removed and bone cement is injected to fill the cavity. Although more time consuming than vertebroplasty the complication rates appear lower with similar potential benefits of both pain relief and improved function to vertebroplasty but with reduced risk of cement leak. There is also the potential to restore vertebral height but this only occurs in a minority of patients. At the present time, the documented use of kyphoplasty in myeloma is limited to case reports and small case series (Fourney *et al*, 2003; Masala *et al*, 2004) although outcomes in myeloma do appear comparable to those in osteoporosis (Lane *et al*, 2004). The UK NICE (NICE, 2003b) reviewed the evidence on kyphoplasty for vertebral compression fractures and made the following recommendations:

- The procedure should only be undertaken where there are good arrangements for access to spinal surgery services in the event of complications.
- The indication and suitability for the procedure should be agreed by the multidisciplinary specialist team.
- Clinicians performing the procedure must have received training to an appropriate level of expertise.
- The procedure should be limited to patients whose pain is refractory to more conservative treatment.

Recommendations

- **The use of vertebroplasty or kyphoplasty may be considered in patients with persistent pain (Grade B recommendation; level III evidence).**
- **The use of kyphoplasty should follow the NICE recommendations summarized above (Grade C recommendation; level IV evidence).**

6. Management of peripheral neuropathy

6.1 Scope

Many patients with myeloma have subclinical or even clinical PN at diagnosis, often due to co-morbidities (see 6.2.2). These patients are at risk of worsening PN when exposed to potentially neurotoxic drug treatments, such as thalidomide and bortezomib. The cause of PN in myeloma patients is multifactorial and when patients are assessed, it is important to grade the degree of neuropathy using a recognized scale, such as the National Cancer Institute (NCI) Common Toxicity Criteria (Trotti *et al*, 2003), LANSS (Bennett, 2001) or the Total Neuropathy Score (Cavaletti *et al*, 2007). Additionally, it may be helpful to evaluate the pain intensity and its effect on functioning, using the 'Worst pain in past week' item (score 0–10) of the Brief Pain Inventory (Shi *et al*, 2009b).

6.2 Causes

PN in myeloma patients can be subdivided as follows:

6.2.1 Disease- or M protein-associated peripheral neuropathy. Spinal cord or nerve root compression is a common neurological complication of myeloma due to compression by plasmacytoma, lytic or extramedullary disease (Silberman & Lonial, 2008) and requires appropriate imaging and specific treatment including a specialist opinion as to the need for surgical intervention or radiotherapy.

The well recognized association between MGUS and PN (Kelly *et al*, 1981; Nobile-Orazio *et al*, 1992) is addressed in the Guidelines for Management of MGUS (Bird *et al*, 2009). The incidence of PN in myeloma is less well documented, with earlier studies indicating that symptomatic PN is present in 3–13% of cases at diagnosis (Silverstein & Doniger, 1963; Walsh, 1971) and subclinical PN in one-third of patients, detectable by nerve conduction or histopathological studies (Kelly *et al*, 1981). The reported prevalence of sensory PN may depend on the study cohort, the methods of detection and the criteria used, with a recent study reporting rates of pre-treatment sensory PN in up to 20% of patients, and neuropathic abnormalities in as many as 54%. (Richardson *et al*, 2009). The cause of the neuropathy in many cases of myeloma is not clear and may be multifactorial, and studies have also varied in relation to rates of small or large fibre or mixed PN. In those cases where amyloidosis and toxicity due to chemotherapy are not the cause, the M protein itself or other consequences of the underlying disease may play a part. Clinically, a symmetrical, distal sensory/motor neuropathy inducing paraesthesiae and numbness in the hands and feet is seen. Treatment of the myeloma results in varying degrees of improvement in the PN in this situation and in some cases the PN may worsen (Kyle, 1992). Given the variation between studies, it is likely that further studies with standardized criteria are warranted to characterize baseline PN in patients with myeloma.

POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, M-protein and Skin abnormalities) syndrome and AL amyloidosis are more specialized situations, PN is a significant clinical feature in 85–100% of patients affected by POEMS syndrome (Dispenzieri & Gertz, 2004). It is a consequence of axonal degeneration and demyelination, typically distal, symmetrical and initially sensory, but as the condition progresses, a disabling symmetrical weakness may develop.

PN affects 17% of patients with AL amyloidosis at diagnosis (Kyle & Gertz, 1995). The PN is typically axonal and characteristically painful, distal and symmetrical and often associated with an autonomic neuropathy. Treatment options for AL amyloidosis are discussed in the BCSH Guidelines (Guidelines Working Group of UK Myeloma Forum, British Commitee for Standards in Haematology and British Society for Haematology, 2004). Cryoglobulinaemia is another recognized source of PN.

6.2.2 Peripheral neuropathy related to co-morbidities. Conditions such as diabetes mellitus, carpal tunnel and other nerve compression syndromes, including chronic inflammatory demyelinating polyradiculoneuropathy, chronic renal failure and vitamin B12 deficiency, should be actively sought and appropriately managed, with specialist input as needed.

6.2.3 Chemotherapy-induced peripheral neuropathy (CIPN). Chemotherapy-induced peripheral neuropathy (CIPN), also known as treatment-emergent peripheral neuropathy, is a major aspect of myeloma management. CIPN has been a long recognized complication of vinca alkaloid and platinum-based treatments (Wolf *et al*, 2008) and may be significantly dose limiting, but these drugs are no longer in regular use in myeloma. There is emerging evidence for the incidence and natural history of PN due to novel therapies, including thalidomide-induced PN (TiPN) (Palumbo *et al*, 2008b) and

bortezomib-induced PN (BiPN) (Argyriou *et al*, 2008), which may be considered as distinct clinical entities.

TiPN may arise after prolonged administration of thalidomide (39–75% of patients of patients treated for 12 months), is mostly mild to moderate in severity (Mileshkin *et al*, 2006) and appears to be a cumulative effect (Cavaletti *et al*, 2004). Initial symptoms include sensory changes, such as paraesthesia and hyperaesthesia, motor symptoms and autonomic dysfunction. Later effects include loss of vibration and joint position sense, which may lead to ataxia and progressive gait disturbance. Nerve conduction studies do not reliably predict the onset of significant TiPN and do not necessarily correlate with the clinical findings (Mileshkin *et al*, 2006). Reduction or temporary discontinuation of the drug usually leads to a clinical improvement in the symptoms whereas continuation of dose intense treatment in the face of neuropathy may cause permanent neurological damage. Mileshkin *et al* (2006) and other investigators have recommended that thalidomide therapy should not exceed 6 months as the risk of TiPN is unacceptably high.

BiPN is characterized by neuropathic pain and a length-dependent distal sensory neuropathy with suppression of reflexes (Cavaletti & Nobile-Orazio, 2007). Motor neuropathy may follow and infrequently results in mild to severe distal weakness in the lower limbs (El-Cheikh *et al*, 2008). There may also be a significant autonomic component, which manifests as dizziness, hypotension, diarrhoea or constipation and/or extreme fatigue. It is thought to occur at a certain threshold (within five cycles but rarely beyond) of treatment (Richardson *et al*, 2006b) and may be more likely to occur within the setting of renal impairment, in keeping with other therapy-related toxicities in this setting (Jagannath *et al*, 2005a). Electrophysiological testing reveals a mainly distal sensorimotor axonal loss, with secondary demyelination. The symptoms of BiPN improve or completely resolve in the majority of patients after a median of 3 months following discontinuation of the drug (Richardson *et al*, 2003, 2006b; Badros *et al*, 2007), but in a proportion of cases, symptoms have taken up to 2 years to improve (El-Cheikh *et al*, 2008). Apart from a graded dose reduction or withdrawal (Richardson *et al*, 2006b), the only treatment for BiPN is symptomatic relief. No effective prophylactic treatment is available and any use of nutritional supplements should be restricted to low doses to avoid harm from excessive doses of pyridoxine (Levine & Saltzman, 2004). In particular, caution should be exercized with supplements containing ascorbic acid, which may inhibit the anti-myeloma effect of bortezomib (Perrone *et al*, 2009).

The frequency of BiPN varies between studies. Data from the SUMMIT (Study of Uncontrolled Multiple Myeloma managed with Proteasome Inhibition Therapy) and CREST (Clinical Response and Efficacy Study of Bortezomib in the Treatment of Relapsing Multiple Myeloma) phase II trials in the relapsed setting suggest that BIPN occurs in about 35% of patients (13% grade 3 and 0·4% grade 4), and led to discontinuation of therapy in 5% and dose reduction in 12% (Richardson *et al*, 2006b; Badros *et al*, 2007). Other studies suggest a higher incidence in up to 75% of patients with relapsed disease and 33% of newly diagnosed patients, while grade 3–4 neurotoxicity may affect 30% of relapsed and 18% of newly diagnosed patients who receive bortezomib (Jagannath *et al*, 2005b; Badros *et al*, 2007).

Table III. Important features of the neurological history.

Sensory symptoms	Motor symptoms	Autonomic symptoms
A sensation of wearing an invisible 'glove' or 'sock'	Tripping on the toes	Orthostatic dizziness
Wooden quality	Loss of grip strength	Constipation
Numbness, pins and needles		Diarrhoea
Feeling of walking on pebbles		Bladder incontinence
Feeling of tightness and swelling		Sexual dysfunction
Burning sensation or freezing pain		Dry eyes
Sharp, jabbing or electric shock-like pain		Dry mouth
Extreme sensitivity to touch		
Usually worse at night		
Loss of balance and coordination		
Cramps in the feet and calves		

Table IV. Investigation of peripheral neuropathy.

Routine	Additional	Consider	Specialist tests
FBC	Serum B12	MRI of spine and plexii (if radicular compression is suspected)	Nerve conduction studies
U&E	Lipids		
LFT	Fasting glucose		Lumbar puncture and CSF protein
Ca		Oral glucose tolerance test	
ThFT	ANA	SAP scan	Anti-neuronal antibodies
	ENA		
	ANCA		Nerve biopsy
	Serum ACE		

FBC, Full Blood Count; U&E, urea and electrolytes; LFT, liver function tests; Ca, Serum calcium; ThFT, thyroid function tests; ANA, anti nuclear antibody; ENA, extractable nuclear antigen; ANCA, Antineutrophil cytoplasmic antibody; ACE, angiotensin converting enzyme; MRI, magnetic resonance imaging; SAP, serum amyloid P; CSF, cerebrospinal fluid.

6.3 Assessment and investigation of peripheral neuropathy

An accurate neurological history should be taken from all patients prior to commencement of neurotoxic agents and regularly during the course of therapy (Table III). Patients should be reviewed in person at the start of each cycle to ensure that emergent symptoms are detected and acted upon. Dose-reductions may be needed within a treatment cycle if symptoms are progressive, so as to avoid the irreversible

neurological damage that may result from waiting until the next cycle to make a change.

It is important to grade the severity of the symptoms of CIPN using a scale, such as the NCI-CTC (Trotti *et al*, 2003), to provide an objective assessment of the PN, so that if different members of the team are assessing the same patient, sequential assessments can made and trends identified.

Initial investigations should be tailored according to the history and examination and may include those listed in Table IV. Vitamin B12 deficiency should be screened for periodically. Metabolic and autoimmune causes should also be considered. If there are prominent features of small fibre neuropathy, then AL amyloidosis should be excluded by tissue biopsy or serum amyloid P (SAP) scan; any further investigations, such as electrophysiological studies or cerebrospinal fluid protein estimation, should be directed by a neurologist.

6.4 Management of peripheral neuropathy

The management of PN should include symptom control along with treatment of any potentially reversible causes. Identification and correction of Vitamin B12 deficiency is important and optimal management of co-morbid causes, such as diabetes mellitus or alcohol excess, may also improve tolerance of neurotoxic drugs. An awareness of the spectrum of symptoms that herald CIPN is crucial. Such symptoms need to be carefully sought at each meeting with the patient.

Careful monitoring of patients receiving bortezomib and prompt dose and schedule modifications are essential. Dose reductions according to the Summary of Product Characteristics (SPC), or changing from twice weekly to once weekly dosing should be instituted as soon as symptoms emerge. Temporary interruptions in therapy may also be beneficial, before resuming on a new schedule/dose. 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 (Mateos *et al*, 2008b; Palumbo *et al*, 2008c; Bringhen *et al*, 2010). Continuation of dose intense treatment in the face of neuropathy may cause permanent neurological damage. Measurement of lying and standing blood pressures weekly in patients receiving bortezomib may detect autonomic neuropathy before it becomes a debilitating problem for the patient. The administration of intravenous normal saline prior to each dose of bortezomib may improve tolerance of the drug.

Neuropathic pain is often poorly responsive to standard analgesic regimes. There has been very little research specifically in the management of painful CIPN, and that has mostly been in solid tumours (Tsavaris *et al*, 2008). Opioids can be effective but if used alone in high dose are associated with significant adverse effects (Rowbotham *et al*, 2003). A multimodal approach using opioids together with other pain modulating drugs is now recommended (Ossipov & Porreca, 2005; Raphael *et al*, 2010b). Thus a calcium channel blocker should be added early (e.g. gabapentin or pregabalin); it may be necessary to add a sodium channel blocking agent, e.g. oxcarbazepine (carbamazepine should be avoided because of drug interactions); or an SNRI, e.g. amitryptiline or duloxetine (Jensen *et al*, 2009).

Several studies have shown that adding gabapentin to an opioid in patients with cancer-related neuropathic pain can give improved analgesia with reduced adverse effects compared to using either agent alone (Caraceni *et al*, 2004; Keskinbora *et al*, 2007; Ho *et al*, 2009). The study of CIPN from (Tsavaris *et al*, 2008) was not randomized but 75 patients who received 800 mg/d of gabapentin were compared to 35 patients who declined gabapentin but received naproxen and codeine/paracetamol instead. Gabapentin led to a complete response in 25·3% of patients (19/75), partial response in 44% (33/75), minor response in 25·3% (19/75), and no response in 5·3% (4/75). In the 'control group', none experienced complete response (0/35), while partial, minor and no response were observed in 5·7% (2/35), 45·7% (16/35), and 48·6% (17/35), respectively. The response to gabapentin correlated with the severity of the underlying neurotoxicity. Approximately 25% of patients receiving gabapentin experienced mild somnolence, but none discontinued it. Note that gabapentin may be associated with myelosuppression and so should be avoided around the time of stem cell transplant.

The haematologist who is not familiar with these agents should seek advice from the local chronic pain or palliative care service. For patients with continuing severe pain in spite of initiating these drugs or those who are unable to tolerate analgesics because of adverse effects, specialist help is essential. They will advise on dose modifications and can also initiate specialist options, such as ketamine, methadone or spinal analgesia.

In addition, topical treatments may be of benefit. Capsaicin cream 0·075% acts on peripheral nerve TRPV1 (transient receptor potential cation channel, subfamily V, member 1) heat and pain receptors; menthol acts on TRPM8 (transient receptor potential cation channel, subfamily M, member 8) receptors for cold and may both be helpful in patients with 'cold' or 'hot' dysaesthesia, respectively (Vriens *et al*, 2008). Emollients, such as cocoa butter, may help some patients but the physiological mechanism is unclear. In other forms of superficial neuropathic pains (e.g. post-herpetic neuralgia or scar pain), the sodium channel blocker lidocaine can be used topically as a 5% plaster, applied to the affected area for 12 h and then left off for 12 h. Some patients obtain relief within a few days but the peak effect is reached with 2–4 weeks (Baron *et al*, 2009; Binder *et al*, 2009).

Recommendations

- **Symptoms and signs of peripheral and autonomic neuropathy should be actively sought using a validated screening tool, such as LANSS, and the cause identified, where possible (Grade C recommendation; level IV evidence).**

- **Clinical evidence of a significant (e.g. >NCI grade 2) or progressive PN at diagnosis should be appropriately investigated to identify treatable causes and referral to a neurologist should be made so that appropriate neurological investigations can be performed (Grade C recommendation; level IV evidence).**
- **The severity of neuropathy should be sequentially graded with a validated tool, such as the Total Neuropathy Score (Grade C recommendation; level IV evidence).**
- **Potentially neurotoxic drug treatments should be used with caution in patients with a pre-existing PN (Grade C recommendation; level IV evidence).**
- **Any patient who develops a significant (e.g. >NCI grade 2) or progressive CIPN should be managed with graded dose reduction or drug withdrawal. Referral to a neurologist for specialist investigation should be considered if there is no improvement or the use of another neurotoxic drug is planned (Grade C recommendation; level IV evidence).**
- **All patients with chronic peripheral neuropathic pain should be considered for multimodal analgesic treatment including an opioid, ion channel blocker and SNRI (Grade A recommendation; level 1b evidence).**
- **Superficial neuropathic pain should be treated with topical lidocaine 5% plaster (Grade A recommendation; level Ib evidence).**
- **Patients with significant uncontrolled neuropathic pain should be referred promptly for specialist advice regarding pain management (Grade C recommendation; level IV evidence).**
- **Routine use of nutritional supplements cannot be recommended due to insufficient evidence for benefit, although deficiencies should be corrected (Grade C recommendation; level IV evidence).**

7. Control of other symptoms

7.1 Nausea and vomiting

7.1.1 Acute emesis. Nausea and vomiting may occur in myeloma patients for many reasons – as symptoms of hypercalcaemia, side-effects of analgesics and toxicities of anti-cancer therapies. Acute onset emesis can usually be managed with dopaminergic prokinetic anti-emetics, e.g. oral domperidone or oral/parenteral metoclopramide. These have minimal side-effects, whereas the anticholinergic cyclizine may be effective but is associated with significant sedation and dry mouth. Note that whereas prokinetics stimulate gastrointestinal motility, cyclizine suppresses it and so it is irrational to use a combination of these simultaneously.

Myeloma patients may be psychologically stressed by the illness and coping with treatment: stress-related hyperacidity and peptic ulceration may occur and be expressed by nausea and vomiting. This is best managed by an oral proton pump inhibitor (PPI).

If emesis does not settle with a dopamine agonist and PPI, then the butryphenone drug haloperidol is usually effective. At doses of, for example, 1·5–5 mg nocte as a single oral or sc dose (+ 0·5–2 mg prn doses) it is usually not sedating. Older people may be more prone to extrapyramidal adverse effects.

If haloperidol is also unsuccessful, then the broad spectrum phenothiazine levomepromazine (Nozinan) may be used. When given at doses of up to 10 mg/d (as a single nocte dose or by 24-h infusion via a sc syringe driver), it is fairly well tolerated – but at higher doses it tends to be sedating, causes hypotension and may be associated with Parkinsonian side-effects. Levomepromazine should therefore be reserved for patients who do not respond to domperidone/metoclopramide or haloperidol.

Acute emesis induced by chemotherapy or radiation therapy can also be managed by agents such as domperidone or metoclopramide, but for the more intensive chemotherapy regimens used in myeloma serotonin (5HT3) receptor antagonists may be considered (Keeley, 2009). Local policies will determine which 5HT3 receptor antagonist is used. Prolonged use of these agents cause troublesome constipation, so they are best reserved for short-term use related to anti-cancer therapies.

Most of the regimens used in myeloma are not 'highly emetogenic' but some patients experience intolerable nausea and vomiting with even less emetogenic combinations. In such cases, the Neurokinin-1 (NK-1) antagonist aprepitant may be used. Aprepitant has to be started, together with dexamethasone, on the day of chemotherapy and is continued on days 2 and 3. It is licensed for highly emetogenic chemotherapy or moderately emetogenic chemotherapy with anthracyline/cyclophosphamide combinations. It is reasonable to consider its use off-licence for other patients who may otherwise refuse further chemotherapy (Kris *et al*, 2006).

7.1.2 Chronic emesis. Nausea and vomiting which does not settle even with the combinations described above may be managed with continuous subcutaneous infusions, delivered by a portable syringe driver, of a combination of metoclopramide and haloperidol, or metoclopramide and levomepromazine. A 5HT3 receptor antagonist may be added for a few days but prolonged use will cause severe constipation. For example, the dose of levomepromazine may be increased up to 25 mg/d, but significant sedation is likely result at this dose. At this level the patient should be referred to a palliative care team. It is important to exclude raised intracranial pressure and other causes for refractory emesis.

7.2 Loss of appetite (anorexia)

Classic cancer cachexia occurs frequently in patients with solid tumours but is uncommon in myeloma. However, many patients do experience periods of loss of appetite and may lose weight. An exceptional case is at the time of high dose chemotherapy and stem cell transplant, when significant

weight loss may occur in a short time (Murray & Pindoria, 2009). Often anorexia is related to stress and psychological adjustment disorders – referral to a specialist nurse for exploration of these issues may be the best first step. A good dietary history should be taken, preferably by a dietician. Patients should be encouraged to take smaller, more frequent meals rather than two large meals per day. Nutritional supplements can be added according to the patient's taste, e.g. milk-based drinks, milkshakes or powders to increase the protein/carbohydrate content of savoury dishes.

Corticosteroids can improve appetite over a few days, but chronic use should be avoided because of their long-term adverse effects. For example, it is reasonable to give dexamethasone 4 mg/d for a maximum of 7 d, tapering off over 1 week. For more prolonged appetite stimulation, the progestogen megestrol acetate can be used at doses of 160 mg bd or tid. At these doses the side-effects of ankle oedema and DVT are minimal (Berenstein & Ortiz, 2005).

7.3 Constipation and diarrhoea

Constipation occurs with great frequency in myeloma patients. It may be a result of hypercalcaemia, or a side-effect of drug therapy with thalidomide, opioids, anticholinergics or 5HT3 receptor antagonists. It is important to review all current medication and minimize drugs that may be causing or aggravating constipation.

Opioid-induced constipation can be reduced by using fentanyl or buprenorphine, which cause much less of this adverse effect, compared to morphine and oxycodone.

Laxative medications are very commonly used but the evidence base for them is not convincing (Ahmedzai & Boland, 2007). It is rational to consider the use of a combination of a stool softener, such as docusate, together with a stimulant, such as senna or codanthrusate. For prevention of constipation, regular macrogol (Movicol, Laxido) or lactulose may be considered.

The management of opioid-induced constipation is likely to be revolutionized in the next few years with the advent of peripherally-acting opioid antagonists (Holzer *et al*, 2009). These novel approaches include slow-release naloxone (available in a combination with slow release oxycodone –Targinact (Schutter *et al*, 2010); and parenteral methylnaltrexone (Thomas *et al*, 2008).

Patients receiving treatment for myeloma may suffer with diarrhoea. Bortezomib and lenalidomide may be associated with diarrhoea and require dose modification or cessation of the drug (Bird *et al*, 2011). Management of diarrhoea should be directed at the underlying cause, but symptomatic measures include antimotility agents, such as loperamide and antcholinergic drugs, such as propantheline (Twycross & Wilcock, 2008).

7.4 Mucositis

Oropharyngeal mucositis occurs frequently in myeloma patients on chemotherapy agents. It is most troublesome during the neutropenic phase of haemopoietic stem cell transplantation (HSCT), when it can lead to complete inability to take oral food or fluids because of the pain and ulceration.

Mucositis may be monitored and measured using a standardized visual rating tool. During HSCT this would reasonably be done at least once a day. Potential management for mild grades of mucositis includes the weak analgesic Difflam mouthwash. There is no place for chlorhexidine mouthwash. More troublesome cases can be managed with oxetacaine/antacid combination, which is swilled round the mouth and then may be swallowed to treat oropharyngeal and oesophageal mucositis. This may have to be given up to 2 hourly in grade 4 cases. Some patients can tolerate lidocaine ice lollies or mouthwashes (Shaiova *et al*, 2004; Potting *et al*, 2006; Peterson *et al*, 2009).

In patients who are at special risk of mucositis, the keratinocyte growth factor palifermin may be used, but it has to be started before chemotherapy (Kobbe *et al*, 2010). Caphasol may also be effective in the setting of high dose therapy (Papas *et al*, 2003).

With grade 1–2 mucositis, the patient may be able to take oral medication, such as an opioid tablet or liquid. Oral transmucosal fentanyl may be effective (Shaiova *et al*, 2004), but many patients with mucositis cannot use this. With more severe grades, a subcutaneous infusion of oxycodone (or morphine) can be given by syringe driver. In the most severe cases, it may be necessary to start an intravenous patient-controlled analgesia (PCA) delivery of opioid – this should be done by the local acute pain team.

7.5 Sedation

Many drugs used in myeloma can cause sedation (thalidomide, opioids, gabapentin, tricyclics, benzodiazepines). In addition, drowsiness may be a feature of hypercalcaemia or of hypoactive delirium. It is important to warn patients of likely sedation when starting new medication and they should be counselled about the risks of taking sedative medication and drinking or driving.

Sedation due to the initiation of opioids sometimes settles in a few days, but often it does not. Fentanyl and oxycodone are less sedating than morphine or other potent opioids and the patient may become more alert within days of changing to these (Ahmedzai & Brooks, 1997; Mucci-LoRusso *et al*, 1998; Clark *et al*, 2004; Reid *et al*, 2006).

If sedation is causing impairment of quality of life, then the patient should be referred to a palliative care team for consideration of a psychostimulant, such as methylphenidate or modafanil (Gagnon *et al*, 2005; Minton *et al*, 2008; Blackhall *et al*, 2009).

7.6 Fatigue

Fatigue occurs in the majority of patients with myeloma and may be a major cause of reduced functioning and quality of

life, although is often under-recognized by professionals. It is usually multifactorial – common treatable causes include anaemia, low testosterone, thyroid deficiency and there many be biochemical abnormalities including secretion of cytokines (Shafqat *et al*, 2005). Often the fatigue is related to sedating medication (see section above). Psychological causes of mental fatigue are common and should be explored by a specialist nurse or in severe cases, by a psychologist or psychiatrist.

There is clinical trial evidence that aerobic exercise programmes and the encouragement of physical activity after bouts of hospitalization, especially for HSCT, are beneficial in terms of mood and physical functioning (Dimeo *et al*, 1997; Coleman *et al*, 2003). Patients should be encouraged to take brisk walks and graded exercises, including swimming. Anorexic patients may improve if given high carbohydrate supplements to boost calorie intake and the state of hydration should be reviewed. It is important to pay attention to sleep patterns, to encourage activity and minimal napping by day, and the avoidance of getting up at night to take refreshments or watch television. Patients should be referred to physiotherapy or rehabilitation services for these programmes.

8. Bisphosphonate-induced osteonecrosis of the jaw (BONJ)

Osteonecrosis of the jaw (ONJ) is an increasingly recognized complication of bisphosphonate therapy and is sometimes called bisphosphonate-induced osteonecrosis of the jaw (BONJ). The first case was described in 2003 (Carter & Goss, 2003) The definition of BONJ is 'the presence of exposed necrotic bone in the mandible or maxilla that does not heal after 2 months in a patient receiving or with prior exposure to a bisphosphonate who has not had radiotherapy.' Typical features are pain and localized infection, loosening of teeth and even spontaneous avulsion and soft tissue ulceration with sinus formation.

The precise aetiology is unclear but is likely to be multifactorial with contributions from a number of factors including infection and vascular insufficiency within the microcirculation. The most common precipitating event is dental extraction. A history of surgical intervention, long term use of bisphosphonates, especially sequential use of intravenous pamidronate/zoledronic therapy, prior history of malignant disease, significant comorbidity, smoking and poor dental health are all recognized risk factors (Boonyapakorn *et al*, 2008), there is also evidence of possible genetic risk factors (Sarasquete *et al*, 2009). Duration of therapy and dosage (exposure) seems to be an important aspect (Mavrokokki *et al*, 2007). The incidence of BONJ with oral bisphosphonates is much less than those administered intravenously (possibly 100 times less). With oral agents, the incidence of BONJ is estimated to be 1:10 000 and 1:100 000 patient years (Khosla *et al*, 2007).

The diagnosis of BONJ is a clinical one. Patients present with pain and evidence of local infection (swelling, pus) although in a minority they are asymptomatic. The lesions are mostly localized to the mandible and over half occur in regions of recent dental extraction. Plain radiographs (OPG panoramic X-rays) can miss the presence of osteomyelitis in the early stages. A biopsy is seldom necessary as are further investigations such as CT, MRI or positron-emission tomography imaging.

The management of BONJ is largely supportive. Symptom control is usually achieved by good oral care with without antibiotics. Occasionally, limited debridement of bone is indicated. There is no consensus as to whether to stop temporarily or discontinue bisphosphonate usage in affected individuals. Patients may develop BONJ up a year after stopping bisphosphonate treatment. Because BONJ tends to be a chronic condition, prevention is paramount and patients at risk should be identified and invasive dental procedures avoided (Barker & Rogers, 2006; Weitzman *et al*, 2007).

Patients should be made aware of the risk of BONJ before embarking on long-term bisphosphonate use. Patients on oral bisphosphonates should be encouraged to see a dentist, however for those commencing intravenous bisphosphonates dental screening is essential (Weitzman *et al*, 2007). Before initiation of IV bisphosphonate therapy the patient should have no expected extractions for the foreseeable future. Any teeth that are likely to require extraction should be removed before starting therapy. Ongoing dental care and maintenance (fillings) can continue with patients on the IV treatment. Patients, who have already received IV therapy and develop dental problems, which might possibly require extractions, should be referred to a specialist. It is important that teeth/roots are retained whenever this is feasible. Although there is little evidence to guide management of bisphosphonate treatment around invasive dental work it would seem reasonable to stop treatment in high risk patients and not recommence treatment until healing has occurred but this approach should be balanced against any ongoing fracture risks due to disease in the individual patient (Badros *et al*, 2008).

Recommendations

- **All patients to be started on long term bisphosphonate treatment should be warned of the risk of BONJ and its predisposing factors (Grade C recommendation; level IV evidence).**
- **All patients to be started on IV bisphosphonate should be referred for a dental opinion and any teeth of poor prognosis extracted before initiation of bisphosphonate therapy. Patients on long-term oral bisphosphonates should have regular dental care and maintain excellent oral hygiene (Grade C recommendation; level IV evidence).**
- **Invasive dental procedures in patients on IV or long-term oral bisphosphonate should be avoided as far as possible. For patients on IV bisphosphonate, a specialist opinion should be sought prior to any extractions (Grade C recommendation; level IV evidence).**

- **Patients with suspected BONJ should be referred to a clinician with special interest and expertise in the management of this condition (Grade C recommendation; level IV evidence).**

9. The role of complementary therapies in the management of myeloma

9.1 Definition

Complementary therapy can be defined as therapies that are used alongside, or integrated with, conventional health care (Tavares, 2003). These differ from alternative therapies, which are designed to be used in place of conventional therapy. However, a clear definition of what constitutes complementary and alternative medicine has not yet been elucidated, and therefore discretion must be exercised when interpreting guidance pertaining to these therapies.

In the UK, research is emerging on the role of complementary therapy in the management of myeloma. To date, the majority of available evidence is anecdotal and policy development is in its infancy. Studies have revealed that >25% of patients with haematological malignancies including myeloma, are using complementary therapy as adjunct to their prescribed conventional treatment (Molassiotis *et al*, 2005a), delivered primarily in hospices, hospitals and throughout the voluntary sector (Tavares, 2003).

Complementary therapy has a role in the management of multiple myeloma when used as adjunct to conventional medicine. It improves patients' perceived quality of life and ability to cope with the effects of the disease. The development of an evidence-base to support complementary therapy use in myeloma is in the early stages of development. Until complementary therapy has undergone rigorous testing in clinical trials, healthcare professionals should exercise caution with their recommendations.

9.2 The patient's preference

Patients with myeloma may express preference for complementary therapy and place value in the role they have to play within the context of their cancer care plan – for the management of both the psycho-social and physiological effects associated with myeloma. Patients may value complementary therapy and the sense of control gained when they are used as part of their cancer treatment plan. Consequently, patient choice should be informed and respected by healthcare professionals in order to ensure the best overall treatment and care plan for myeloma is delivered.

Healthcare professionals should recognize that within the myeloma care plan, patient treatment preference, choice and need for reliable information is critical such that complementary therapy is accessed safely, should a patient wish to do so. In line with the NICE recommendations for Improving Supportive and Palliative Care for Adults with Cancer (NICE, 2003b), the healthcare community must work within their Cancer Network to ensure availability of high quality information for complementary therapy, where there is evidence to support its use.

9.3 Potential benefits of complementary therapy

There is a dearth of scientific evidence to support the effectiveness of complementary therapy in the management of myeloma; however, some studies have shown that complementary therapy can help patients with myeloma to: manage their symptoms, live with altered body image, promote relaxation, alleviate anxiety, reduce chemotherapy side-effects, improve sleep pattern, reduce stress and tension, reduce psychological distress/provide emotional support and improve well-being (Molassiotis *et al*, 2005a; Leukemia and Lymphoma Society, 2006). Importantly, cancer patients using complementary therapy also perceive an improved quality of life (Tovey *et al*, 2005).

Some complementary therapies, such as acupuncture, have been submitted to more rigorous evaluation and are acknowledged for their effective use in cancer treatment for the management of chemotherapy-associated nausea and vomiting (National Institutes of Health Consensus Statement, 1997). However, no convincing scientific-evidence has emerged to date that shows complementary therapy slows cancer progression (Leukemia and Lymphoma Society, 2006).

9.4 Commonly used complementary therapies

The types of complementary therapies and frequency with which they are used by myeloma patients vary considerably. Among the most common therapies are homoeopathy, touch therapies such as aromatherapy, massage and reflexology, healing and energy therapies such as reiki, spiritual healing and therapeutic touch, hypnosis and hypnotherapy, acupuncture, herbal medicines and dietary interventions (Molassiotis *et al*, 2005b). Examples of the latter include green tea and curcumin, two chemoprotective agents shown to induce cellular apoptosis in myeloma (Bharti *et al*, 2003; Nakazato *et al*, 2005; Shammas *et al*, 2006; Liu *et al*, 2007; Hatcher *et al*, 2008) and currently gaining credibility as effective complementary therapies for myeloma. In addition, as covered in section 6.4, some topical treatments have a physiological basis in providing symptomatic relief in painful PN (Vriens *et al*, 2008). However, caution should be exercised with some nutritional supplements. For example, there is evidence that nutritional supplements containing ascorbic acid (vitamin C) may inhibit the anti-myeloma effect of bortezomib and should be avoided at least on the days of bortezomib administration (Perrone *et al*, 2009).

Recommendations

- **Complementary therapy can offer benefit to myeloma patients when integrated with conventional medical treatments (Grade B recommendation; level IIb evidence)**

- **Patients, carers and healthcare professionals should have access to high-quality information on the role of complementary therapy in the management of myeloma. Reputable support organizations, such as Myeloma UK, are a potential source of this information (Grade C recommendation; level IV evidence)**
- **Healthcare professionals should be aware of and prepared to appraise their patient's choice and preference for complementary therapy (Grade C recommendation; level IV evidence).**
- **Careful consideration should be applied by healthcare professionals before recommending complementary therapy until a rigorous evidence-base is developed (Grade C recommendation; level IV evidence).**

10. End of life care

10.1 Definitions

End of life care has recently been the subject of a major review by the NHS, leading to an end of life strategy (Department of Health, 2008). It is likely that all commissioning bodies and acute hospital trusts will be undertaking regional and local reviews of their end of life care provision. Local policies and guidelines are being drawn up and so this section will cover the main concepts only.

Definitions relating to the 'end of life' vary. The 'end of life' strategy (http://www.endoflifecareforadults.nhs.uk) applies to patients in their last months or even years of life, but it does not provide unequivocal definitions. The 'end of life care pathway' [e.g. Liverpool EOL CP (http://www.mcpcil.org.uk/liverpool-care-pathway)] comes into action when the individual is thought to have 24- to 48-h prognosis. It is easy for these terms to be misapplied and there is a possibility for patients and carers to be upset by referral to the wrong agency.

10.2 Recognition of end of life

In myeloma care, it is important for clinicians and teams to recognize when a patient has advancing and untreatable disease to the point that death is likely to occur within the next 12 months. Usually this is evident by relapse, which is confirmed by investigations including bone marrow, blood counts, biochemistry, paraprotein levels, and imaging. At this point, which should be a joint decision of the MDT, it is reasonable to refer the patient to a palliative care team if this has not already been done. This will allow for a palliative care team member to become acquainted with the patient even if he or she does not have significant symptom needs at the present. A holistic needs assessment by the referring team or by the palliative care team can highlight new problems and issues apart from symptoms, e.g. psychosocial difficulties, existential concerns and decisions regarding future care.

One of the UK government's 'end of life' programmes is about 'Preferred Priorities for Care' (PPC; http://www.endoflifecareforadults.nhs.uk/tools/core-tools/preferredprioritiesforcare). This includes eliciting the patients and carers' views and preferences for where the remaining care should be (i.e. home, hospital or hospice, or often a combination); what treatments the patient would want to have or avoid having; and the patient's views on cardiopulmonary resuscitation.

The results of these discussions should be conveyed to the general practitioner (GP), as patients with advanced cancer are now being placed by GPs on their registers for further community-based follow-up, in accordance with the so-called 'Gold Standards Framework' (http://www.goldstandardsframework.nhs.uk).

10.3 Continuation of anti-cancer and other active therapies

The withdrawal of anti-cancer treatment may be seen by many patients as a severe blow to morale and it is essential for this discussion to be held in the presence of family members and a specialist nurse. It should be followed up by a discussion of the patient's and carers' preferences for future care, including the place of care towards the end of life and the use of life-maintaining therapies.

In myeloma management, it is possible to keep offering the patient further forms of treatment aimed at reducing bone marrow plasma cell activity and consequent expression of myeloma symptoms. Even when the patient is approaching the terminal stage (last weeks of life) and specific anti-cancer treatments have been withdrawn, blood and platelet transfusions can be helpful in maintaining quality of life by relieving exertional dyspnoea and preventing bleeding. Management of hypercalcaemia and the maintenance of hydration can be very helpful to prevent symptoms and the onset of renal failure. In occasional patients, management of symptomatic hyperviscosity with regular plasma exchange may be reasonable, and may permit safe transfusion of blood.

If the patient is referred to a palliative care service at this stage, it is helpful for the haematology team to continue to share the care by offering admissions for blood or platelets and other more invasive measures, which may be problematic in a palliative care setting such as many hospices. However, after each blood or platelet transfusion at this stage, it is important for the patient to be asked how worthwhile it has been, as a point may be reached when the patient would actually prefer not to have further transfusions as the benefits do not outweigh the difficulties associated with hospital admission.

At this stage, the balance of responsibility for care may change significantly between GP, hospital and community palliative care teams, although the haematology team, and the patient's clinical nurse specialist (CNS) in particular, often provide continuity of care.

10.4 Last days of life

The term 'last days of life' is preferred to 'end of life' at this stage, as it focuses the attention of the team and the family on the patient's main priorities (and also, as mentioned above, 'end of life' can also refer to the last years of life in chronic disease). This stage is reached when the patient has become increasingly bedbound, profoundly anorexic, weak and spending increasing time at reduced levels of consciousness. Pain and other symptoms may become refractory to previously satisfactory management, in which case a palliative care team should be called upon if the patient is in hospital. It should be noted that family carers and dependents have their own needs at this stage of illness and the haematology CNS, together with the palliative care team, social services and primary care team, should look for and address these needs. Therefore both the patient's and family's holistic needs have to be screened at regular intervals once the patient enters the terminal stage (NICE, 2004).

Specific issues which need attention in the last days of life include –

- Initiation of the 'end of life' (better called 'last days of life') pathway. Most hospitals should now have a policy on how to implement this process, which is a quality assurance tool to ensure that inappropriate medications and obtrusive observations are stopped and all important symptoms are covered by regular or prn prescribing. The pathway also checks if the patient's wishes for a final place of care and other preferences are being met, where possible. Very importantly, the pathway also helps the caring team to recognize the needs of family members for information, emotional and social support and can prepare the way for bereavement support for those who need it.
- For prn medication, a subcutaneous butterfly cannula may be placed to avoid repeated skin punctures
- For regular medication, one or more syringe drivers may be started to give drugs that can be delivered subcutaneously.
- Fentanyl or buprenorphine patches, if already started, should preferably be left in place, and additional pain medication given by oral or subcutaneous route.
- For patients who become unconscious and start to make the 'death rattle', this can be alleviated by positioning and judicious suctioning to remove pharyngeal (not tracheal) mucus, while injections or an infusion of an anticholinergic drug, such as hyoscine butylbromide (Buscopan) or glycopyrrolate should be started to prevent further mucus secretion.
- The roles and needs of family and others close to the patient require recognition and support.

11. Conclusions – the 'holistic needs assessment' and clinical research parameters

In conclusion, patients with myeloma not only require treatments directed at their disease activity but also a wide range of supportive and palliative measures to optimize quality of life at all stages of their disease. Most aspects of myeloma management can be addressed and delivered by the treating haematologists, but collaboration may be required from other relevant specialists. The demands of effective supportive and palliative management are variable between patients and present significant challenges for treating haematologists and other health professionals. Levels of unmet supportive care needs have been identified in a quarter of patients with myeloma and a third of their partners, with significant components of anxiety and depression in both groups (Molassiotis *et al*, 2011).

The UK NHS NICE Guidance for Supportive and Palliative Care for adults with cancer (NICE, 2004) recommends that all cancer patients should have an 'holistic needs assessment' at key points in their trajectory, i.e. at diagnosis, after initial treatment, during follow-up. The specification for how to measure holistic needs in cancer patients was produced by the Kings College Department of Cancer Nursing (Richardson, 2006). One useful instrument for this purpose is the 'SPARC' (Sheffield Profile for Assessment and Referral for Care) tool, which is completed by the patient. It identifies and scores needs with respect to uncontrolled pain and other symptoms as well as psychosocial, spiritual, financial and other issues, using a 4-point verbal or Yes/No rating scale (Ahmed *et al*, 2009). An alternative approach is the Distress Thermometer, which rates overall distress on a numerical analogue scale (Ransom *et al*, 2006).

The increasing survival of myeloma patients and associated symptom burden raises the need for clinical research to run in parallel to novel approaches to controlling disease. Patients in clinical trials will usually need a formal tool for assessing symptoms and their response to treatments. The recommended method is use of the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 generic quality of life questionnaire, together with its myeloma-specific module [QLQ-MY20 (Cocks *et al*, 2007)]. A new instrument has been developed by the EORTC for the measurement of pain arising from bone metastases (Chow *et al*, 2009) which may be useful in some settings. Lessons learnt from the field of late effects of cancer and its treatments (Eiser *et al*, 2007), conventionally applied to curable malignancy, may be of increasing importance in the ongoing management of long term survivors of myeloma.

Recommendations

- **All patients should be assessed for unmet holistic needs at key times in the disease trajectory, preferably using a formal patient-rated tool such as SPARC or the Distress Thermometer (Grade C recommendation; level IV evidence).**
- **For research studies, the EORTC family of quality of life instruments should be used (Grade B recommendation; level IIb evidence).**
- **The recommendations in these guidelines based on level II–IV evidence identify areas where there is scope for future research (Grade C recommendation; level IV evidence).**

Disclaimer

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the UK Myeloma Forum (UKMF), the British Society for Haematology (BSH) nor the publishers accept any legal responsibility for the content of these guidelines.

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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Appendix I: levels of evidence and grades of recommendation

Levels of evidence

Ia	Evidence obtained from meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained from at least one well-designed, non-randomized study, including phase II trials and case-control studies
IIb	Evidence obtained from at least one other type of well-designed, quasi-experimental study, i.e. studies without planned intervention, including observational studies
III	Evidence obtained from well-designed, non-experimental descriptive studies. Evidence obtained from meta-analysis or randomized controlled trials or phase II studies which is published only in abstract form
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Grades of recommendation

Grade A Evidence level Ia, Ib	Recommendation based on at least one randomized controlled trial of good quality and consistency addressing specific recommendation
Grade B Evidence level IIa, IIb, III	Recommendation based on well conducted studies but no randomized controlled trials on the topic of recommendation
Grade C Evidence level IV	Evidence from expert committee reports and/or clinical experiences of respected authorities

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