

Guidelines for screening and management of late and long-term consequences of myeloma and its treatment

John A. Snowden,^{Writing Group Chair^{1,2}} Diana M. Greenfield,^{2,3} Jennifer M. Bird,⁴ Elaine Boland,⁵ Stella Bowcock,⁶ Abigail Fisher,⁷ Eric Low,⁸ Monica Morris⁸ and Kwee Yong,⁷ Guy Pratt⁹ on behalf of the UK Myeloma Forum (UKMF) and the British Society for Haematology (BSH).

¹Department of Haematology, Sheffield Teaching Hospitals NHS Foundation Trust, ²Department of Oncology and Metabolism, University of Sheffield, ³Department of Oncology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, ⁴University Hospitals Bristol NHS Foundation Trust, Bristol, ⁵Palliative Medicine, Queen's Centre for Oncology and Haematology, Hull and East Yorkshire Hospitals NHS Trust, Hull, ⁶King's College Hospital NHS Foundation Trust, ⁷University College London, London, ⁸Myeloma UK, Edinburgh, and ⁹University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

Summary

A growing population of long-term survivors of myeloma is now accumulating the 'late effects' not only of myeloma itself, but also of several lines of treatment given throughout the course of the disease. It is thus important to recognise the cumulative burden of the disease and treatment-related toxicity in both the stable and active phases of myeloma, some of which is unlikely to be detected by routine monitoring. We summarise here the evidence for the key late effects in long-term survivors of myeloma, including physical and psychosocial consequences (in Parts 1 and 2 respectively), and recommend the use of late-effects screening protocols in detection and intervention. The early recognition of late effects and effective management strategies should lead to an improvement in the management of myeloma patients, although evidence in this area is currently limited and further research is warranted.

Keywords: myeloma, late effects, quality of life, haematopoietic stem cell transplantation, chemotherapy.

Methodology

These guidelines were developed using the following stages:

- Review of key literature from 1 April 2006 to 31 March 2016 using the Cochrane database (search term: myeloma) and Medline: search terms used were [myeloma] + late effects, long term effects, frailty, geriatric assessment, infection, infection prophylaxis, vaccination, nutrition, exercise,

rehabilitation, employment, endocrine, disability, late treatment consequences, cancer survivorship (for all papers); and psychological, fatigue, second primary malignancy, quality of life, infection (reviews). As organ-specific areas, such as renal and bone, have been covered in previous guidelines, searches were not re-performed.

- Development of key recommendations based on randomised, controlled trial evidence. In the absence of randomised data, recommendations were developed on the basis of literature review and a consensus of expert opinion.
- Updating of the levels of evidence and grades of recommendation using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) nomenclature for assessing the quality of evidence and providing strength of recommendations (Appendix; <http://www.gradeworkinggroup.org/index.htm>).
- Review of the manuscript was performed by the British Society for Haematology (BSH) Guidelines Committee and Haemato-Oncology Task Force, and the BSH sounding board, comprised of 50 or more members of the BSH who have reviewed this Guidance and commented on its content and applicability in the UK setting, consistent with the primary target audience of UK-based multidisciplinary clinical teams treating myeloma and its complications. Involvement of patient perspectives was through Myeloma UK.
- In preparing these guidelines, the authors have considered overall cost-effectiveness and budget impact of recommended interventions as well as clinical efficacy data and the burden/impact on patients. Formal health economic assessments have not been carried out.

Introduction

As well as aiming to prolong life, modern cancer care needs to address the side effects of treatment, comorbidities and the impact of the physical disease and its treatment on psychological and social wellbeing (Ahmedzai & Walsh, 2000).

Correspondence: BSH Administrator, British Society for Haematology, 100 White Lion Street, London N1 9PF, UK.
E-mail: bshguidelines@b-s-h.org.uk

Guideline

In many cancers, late physical and psychosocial consequences following completion of treatment are increasingly recognised. These 'late effects' have been defined by the US National Cancer Institute (NCI) as: '[A] health problem[s] that occur[s] months or years after a disease is diagnosed or after treatment has ended. Late effects may be caused by cancer or cancer treatment. They may include physical, mental and social problems, and second cancers' (<http://www.cancer.gov/dictionary>).

With the improved outcomes for a range of cancers, increasing attention is merited for late disease and treatment effects and their impact on patient experience (Denlinger *et al*, 2014). Late effects are increasingly relevant to myeloma patients, given that they can often live for over a decade post-diagnosis, have repeated lines of complex therapies and have long-term disease control in the absence of cure.

Late effects in myeloma

Life expectancy for myeloma patients has increased significantly in the last 10–20 years (Renshaw *et al*, 2010). The 5-year relative survival rate for England rose from 19.9%/21.8% (men/women) in 1991–1995 to 37.1% (both sexes) in 2005–2009 and 42.2% (both sexes) in 2007–2011; and the 10-year rate from 8.9%/9.8% (men/women) in 1991–1995 to a level for England and Wales for 2007 of 19.0%/14.9% and 36.6%/28.1% (men/women) in England in 2010–11 (Office for National Statistics, 2011; <http://www.cancerresearchuk.org/cancer-info/cancerstats/types/myeloma/survival/#source2> [Accessed 21 July 2014]). Similar levels of improvement have been shown for the other countries of the UK (Woods *et al*, 2010), and survival rates for patients diagnosed today may be underestimated on the basis of current data (<http://www.cancerresearchuk.org/cancer-info/cancerstats/types/myeloma/survival/#source2> [Accessed 21 July 2014]).

Increased life expectancy is mainly due to the availability of novel chemotherapeutic agents, particularly the proteasome inhibitors and immunomodulatory agents, and the adoption of haematopoietic stem cell transplantation (HSCT) (Klepin & Hurd, 2006; Bird *et al*, 2011; Cook *et al*, 2014; Pratt *et al*, 2014) as well as earlier diagnosis and improved supportive care (Snowden *et al*, 2011).

The physical health of a patient with myeloma is complex, reflecting the effects of the disease, other comorbidities, frailty and the ageing process. Myeloma treatments also have side effects, which may involve permanent organ damage. Patients with myeloma typically undergo courses of treatment followed by periods of stable remission and relapse, although the increasing use of consolidation and maintenance now means that many may remain on treatment for prolonged periods of time during disease stability. The toxicity of multi-drug regimens may combine with the effects of the disease, other comorbidities and the ageing process to diminish physical, psychological and social functioning. Fatigue and pain (predominantly neuropathic and/or bony)

(Osborne *et al*, 2012; Boland *et al*, 2013; Jordan *et al*, 2014) are the common symptoms for myeloma patients and the drugs used to treat pain add to the burden of fatigue and other side effects, further reducing quality of life (Bilotti *et al*, 2011a,b; Snowden *et al*, 2011; Osborne *et al*, 2012; Boland *et al*, 2013; Jordan *et al*, 2014; Sloot *et al*, 2015). Infections are common, especially during active disease and following HSCT (Bilotti *et al*, 2011a,b; Snowden *et al*, 2011), and are a major cause of morbidity and mortality.

This leads to a complex burden for the patient and their family, and a high impact on psychosocial wellbeing and health-related quality of life (HRQoL). Given the extended duration of life and cumulative effects, the burden is often greatest in those with advancing age and multiply-relapsed disease.

The case for screening and management of late effects in myeloma

A key principle of the National Health Service (NHS)-based National Cancer Survivorship Initiative (NCSI; England only) is improving management of the consequences of treatment, from diagnosis onwards (Richards *et al*, 2011a). Likewise, 'survivorship', defined by the NCI, 'focuses on the health and life of a person with cancer post treatment until the end of life. It covers the physical, psychosocial, and economic issues of cancer, beyond the diagnosis and treatment phases' (<http://www.cancer.gov/dictionary>).

The combined late effects of myeloma and its treatment constitute a unique syndrome. Survivorship in myeloma therefore requires specialised screening, coordinated management and multidisciplinary care. British Committee for Standards in Haematology (BCSH)/UK Myeloma Forum (UKMF) guidelines for diagnosis and management (Bird *et al*, 2011; Pratt *et al*, 2014) and for supportive care (Snowden *et al*, 2011) in myeloma have been published and the National Institute for Health and Care Excellence (NICE) have also produced guidelines for myeloma management (NICE 2016). Aspects of survivorship in myeloma have been previously identified by North American authors as areas of significant need for care, and screening guidelines have been developed for detection of late complications relating to novel therapies and HSCT (Bertolotti *et al*, 2008; Faiman *et al*, 2008; Smith *et al*, 2008; Tomlyn *et al*, 2009; Bilotti *et al*, 2011a,b; Richards *et al*, 2011a,b; Majhail *et al*, 2012; Majhail & Rizzo, 2013). However there is no comprehensive, multidisciplinary guideline document for the screening, management and long-term care of myeloma patients.

Aims

These guidelines highlight the key late effects and broader treatment consequences of myeloma, and make recommendations for screening and management of all patients from the start of therapy, along with other appropriate measures

to optimise quality and quantity of life. They are directed primarily at myeloma clinicians and their teams in secondary care, but also provide a reference for primary care clinicians and other hospital-based specialists who will inevitably be involved in ongoing patient management. As this is a clinical guideline, no formal economic evaluation has been performed and local arrangements will determine delivery of care.

Part 1. Long-term physical consequences

Infection and immunity in myeloma

Myeloma causes profound immunodeficiency, which varies during the disease course and, for most patients, lasts lifelong. The immunodeficiency involves numerical and functional defects of B cells, T-cell subsets, natural killer cells, dendritic cells (Brown *et al*, 2001; Ogawara *et al*, 2005; Schutt *et al*, 2006) and, possibly, neutrophil function. This is compounded by the immunomodulatory effects of high-dose corticosteroids and novel agents, neutropenia and host factors, such as immobility.

Most myeloma patients ultimately die of infection-related causes and immunosuppression is directly related to disease activity (Table I). Approximately 10% of patients die within 3 months of diagnosis and infections are often due to encapsulated bacteria (Augustson *et al*, 2005). Atypical infections [e.g. cytomegalovirus (CMV), *Pneumocystis jirovecii*, cryptococcus] are increasingly seen in late-stage heavily treated patients (Teh *et al*, 2013). Most infections are not fatal but may have a major effect on HRQoL. These guidelines exclude the peri-HSCT period because specific guidelines already exist (Majhail & Rizzo, 2013; Rubin *et al*, 2014).

Prophylactic anti-infective drugs. Insufficient data are available to recommend prophylactic antibiotics routinely at any

stage of myeloma (NICE, 2016), although their importance is well recognised in patients with other causes of immunodeficiency, such as neutropenia, following chemotherapy. Trials of co-trimoxazole *versus* placebo or ciprofloxacin or co-trimoxazole *versus* placebo in newly-diagnosed myeloma patients have shown limited benefits of co-trimoxazole, but were too small to draw reliable conclusions (Oken *et al*, 1996; Vesole *et al*, 2012). The current 800-patient TEAMM trial (Tackling EARly Morbidity and Mortality in myeloma), which compares prophylactic levofloxacin with placebo in newly diagnosed myeloma patients, may address these issues (ISRCTN 51731976). Pomalidomide treatment is associated with 23–30% risk of infection and it has been suggested that prophylactic antibiotics could be given for the initial 3 months of therapy (Dimopoulos *et al*, 2014). Ciprofloxacin and enoxacin should be used with caution, as they can interact via cytochrome pathways, but levofloxacin, moxifloxacin, norfloxacin and ofloxacin are safe.

Myeloma patients have an increased risk of viral infections, especially herpes zoster and influenza (Blimark *et al*, 2015). Proteasome inhibitors, immunomodulatory drugs (IMiDs) and high-dose corticosteroids increase this risk, particularly for herpes zoster reactivation (Chanan-Khan *et al*, 2008; Kim *et al*, 2008). Reactivation is greatly reduced by routine antiviral prophylaxis during bortezomib and lenalidomide treatment (Pour *et al*, 2009; König *et al*, 2014; Kouroukis *et al*, 2014), which should be continued for at least 6 weeks after stopping treatment (Terpos *et al*, 2015). Consider continuing aciclovir indefinitely for patients with previous shingles [400 mg once daily (Pour *et al*, 2009; Vickrey *et al*, 2009); or 200 mg once daily in the presence of renal impairment (Minarik *et al*, 2012)].

Invasive fungal infection is rare in myeloma (Chanan-Khan *et al*, 2008; Nucci & Anaissie, 2009) but oropharyngeal candidiasis can occur with prolonged corticosteroid therapy.

Table I. Myeloma timeline: periods of severe immunosuppression and associated common pathogens.

Period	Immunological effects	Common pathogens
At diagnosis and at times of aggressive relapse	Disease active; profound immunosuppression	Bacterial infections, especially <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> and <i>Escherichia coli</i>
Immediate post-autologous stem cell transplant period (c. 1 month)	Neutropenia	Bacteria associated with neutropenic sepsis
Recovery post autograft (up to c. 6 months)	Gradual reconstitution of T cell-mediated immunity	<i>Pneumocystis jirovecii</i> HSV, VZV, CMV; rarely invasive fungal infection
Remission	Immunity improved	Appropriate time for elective vaccinations Re-vaccination schedule >6 months after autograft
Multiple relapses, increasingly refractory disease	Progressive immunosuppression from underlying disease and multiple therapies	Bacteria as above, but in addition: progressive diminution in resistance to viral infections especially HSV, VZV, influenza, occasional atypical infections, e.g. aspergillus, CMV, cryptococcus

HSV, herpes simplex virus; VZV, varicella zoster virus; CMV, cytomegalovirus.

Guideline

Recommendations on the use of intravenous immunoglobulin in myeloma are hampered by insufficient data (Hargreaves, 1992; Chapel *et al*, 1994; Musto *et al*, 1995; Raanani *et al*, 2009; NICE, 2016) but suggest a possible benefit of immunoglobulin for patients in plateau phase.

Intravenous immunoglobulin can increase levels of antibodies to common pathogens in myeloma patients (Morell & Barandun, 1988; Sklenar *et al*, 1993; Raanani *et al*, 2009; Thurnmann *et al*, 2011; Kobold *et al*, 2012). The appropriateness of immunoglobulin replacement should be assessed in terms of infection history, comorbidities, hypogammaglobulinaemia and failure to respond to vaccination. Immunoglobulins should be administered in accordance with national guidance (<https://www.gov.uk/government/publications/clinical-guidelines-for-immunoglobulin-use-second-edition-update>).

Vaccination. The response to all vaccines is typically reduced in myeloma patients. Response is heterogeneous and despite blunted responses, there appears to be clinical benefit (Musto & Carotenuto, 1997; Esposito *et al*, 2010; Cheuk *et al*, 2011). Ideally, functional antibody levels should be used to measure response and inform further vaccination, but guidance in this area is lacking.

Clear recommendations on the timing of vaccination are impossible through lack of data, but vaccinating a myeloma patient while on treatment or with active disease is likely to be less effective (Schmid *et al*, 1981; Hinge *et al*, 2012; Kobold *et al*, 2012; Public Health England, 2013a) than during remission off therapy. Deferring vaccination may not be practical, e.g. seasonal flu vaccination, and may still have some efficacy (Schmid *et al*, 1981; Cheuk *et al*, 2011).

Myeloma patients should only receive inactivated vaccines (Table II). Live attenuated vaccines [Bacillus Calmette–Guérin (BCG), measles, measles/mumps/rubella (MMR), oral typhoid, herpes zoster, rubella, yellow fever] should be avoided.

Table II. Common inactivated vaccines suitable for myeloma patients.

- Diphtheria, tetanus and polio*
- *Haemophilus influenzae* b (Hib)
- Hepatitis A
- Hepatitis B
- Influenza†
- Meningococcal
- Pneumococcal (PCV13 + PPV23)‡
- Typhoid injection (but NOT the vaccine given by mouth)
- Pertussis

PCV13, conjugate pneumococcal vaccine; PPV23, pneumococcal polysaccharide vaccine.

*Oral live polio vaccine (OPV) is no longer available for routine use in UK and should not be used.

†Influenza vaccines in the UK are inactivated. This may not apply in other countries.

‡See text.

It is recommended that all myeloma patients are vaccinated yearly against influenza. Consider vaccinating close household contacts with both the influenza and the varicella-zoster vaccine (Public Health England, 2015). It is recommended that myeloma patients receive the conjugate pneumococcal vaccine (PCV13), followed by the polysaccharide PPV23 at least 2 months later. Those who have already received a single dose of PPV23 should be offered PCV13 at least 6 months after the PPV23, to reduce the risk of pneumococcal serotype-specific hyporesponsiveness (Public Health England, 2013b). The *Haemophilus influenzae* type b vaccine (Hib) should also be considered (Nix *et al*, 2012). Following autologous or allogeneic HSCT, patients are advised to follow a re-vaccination schedule according to the relevant guidelines for patients undergoing HSCT (NICE, 2016).

Recommendations

Assessment.

- Offer patients education so that they can readily recognise infection, understand its implications and seek help (Grade 1C).

Management.

Prophylaxis

- Routinely, antibiotic prophylaxis is not recommended (Grade 2B).
- Offer routine prolonged antiviral prophylaxis against herpes zoster to patients receiving proteasome-based treatments (until at least 6 weeks post-treatment) and post-haematopoietic stem cell transplantation (HSCT) (Grade 1A) and consider for those taking both immunomodulatory drugs with high-dose corticosteroids (Grade 1C). Consider lifelong prophylaxis for those with previous shingles (Grade 2C).
- Consider intravenous immunoglobulin replacement based on infection history, hypogammaglobulinaemia, comorbidities and vaccination response and in accordance with national guidance (Grade 1C).

Vaccination

- Do not offer live attenuated vaccines at any stage of myeloma (Grade 1B).
- Ideally, offer vaccination during periods of minimal disease and when recovered from treatment (Grade 1B).
- Offer seasonal inactivated influenza and a single course of pneumococcal vaccination (PCV13 followed by PPV23) (Grade 1C).
- Consider *Haemophilus influenzae* (Hib) vaccination (Grade 2B).
- Offer a specific schedule of re-vaccination for patients who have undergone autologous or allogeneic HSCT (Grade 2B).
- Consider vaccination against influenza and herpes zoster for patients' close contacts (Grade 2C).

Renal and urogenital complications

Renal impairment occurs in up to 50% of myeloma patients and is common at presentation. Patients presenting with renal failure are at high risk of early death (Augustson *et al*, 2005). Causes include cast nephropathy, infection, dehydration, hypercalcaemia, hyperuricaemia and renal involvement with AL amyloidosis, and possibly with use of non-steroidal anti-inflammatory drugs (Bird *et al*, 2011). Aggressive early management of these factors and urgent treatment of the underlying myeloma often improves renal function. However, even with initial improvement, patients presenting with renal impairment have a higher chance of developing worsening renal impairment at relapse. The risk of irreversible renal failure increases markedly with time.

Haemorrhagic cystitis may be caused by cyclophosphamide or infections, particularly after HSCT, but is usually short-lived and self-limiting. The immune defect in myeloma can make recurrent urinary tract infections problematic; these infections and their treatment can result in further deterioration of renal function.

About 10% of patients need long-term renal supportive therapy, which can have an impact on HRQoL (Tariman & Faiman, 2010), the range of available therapies for treatment of the myeloma, and survival. Chronic kidney disease (CKD) can be exacerbated by exposure to aminoglycosides, intravenous contrast agents and drugs used to treat CMV reactivation. Appropriate dose reductions need to be followed (Pratt *et al*, 2014) in order to avoid excessive toxicity, such as myelosuppression. Autologous HSCT is still a treatment option in patients with renal impairment, but has to be considered in the context of other frailties and comorbidities and with consideration of dose reduction in melphalan (most commonly to 140 mg/m²) (Saunders *et al*, 2014).

Patients with CKD are at a higher risk than other patients of extra-renal complications, such as anaemia, infection and bone loss, which may best be managed collaboratively with specialists in renal medicine. Anaemia can be treated by blood transfusion or erythropoiesis-stimulating agents (ESAs). ESAs are recommended for anaemia in patients with myeloma-associated renal impairment (Locatelli *et al*, 2004).

Recommendations

Assessment.

- Offer patients information on maintenance of renal health, and promptly investigate any deterioration in renal function not obviously due to myeloma relapse (Grade 1B).
- Routinely monitor patients with chronic kidney disease (CKD) for serum calcium, parathyroid hormone and vitamin D (Grade 1B).

- Investigate anaemia in myeloma patients and monitor long-term for functional iron deficiency (Grade 1C).

Management.

- Refer patients with moderate/severe renal impairment (CKD \geq stage 3), renal-related hyperparathyroidism or nephrotic syndrome to a renal specialist (Grade 1C).
- Optimise diabetes and blood pressure control to reduce the risk of progression to end-stage renal disease (Grade 1B).
- Follow recommended dose modifications for lenalidomide and bisphosphonates in the case of renal impairment and avoid nephrotoxic drugs if possible (Grade 1B).
- Consider erythropoiesis-stimulating agents (ESAs) for myeloma-related anaemia, with iron supplementation as necessary (Grade 1B).

Bone, endocrine and metabolic disorders

Bone loss is a well-recognised complication of myeloma, intensive chemotherapy and corticosteroid usage; vitamin D deficiency, inactivity, hypogonadism, renal failure and secondary hyperparathyroidism and radiotherapy may also contribute. Features include pain, diffuse and localised osteopenia and osteoporosis, fractures and nerve root and cord compression. Most myeloma patients are routinely treated from the outset with bisphosphonates. Zoledronic acid, the current standard of care, has been shown to reduce skeletal-related events, preserve bone density and prolong progression-free and overall survival (Morgan *et al*, 2013). Preservation of bone also requires calcium and vitamin D supplementation, hormone replacement therapy and minimisation of exposure and duration of corticosteroid therapy and chemotherapy (Diamond *et al*, 2010; Miceli *et al*, 2011; Snowden *et al*, 2011).

Intensively treated myeloma patients show a high frequency of endocrine abnormalities, including hypothyroidism (in 9%) and hypogonadism (65% of males). Adrenal function appears to be relatively resilient despite previous pulsed high-dose corticosteroid therapy. Menopause may be precipitated in younger female myeloma patients by chemotherapy and/or radiotherapy. The prevalence of persistent male hypogonadism following intensive treatment raises a need for routine screening and appropriate advice from endocrine specialists (Greenfield *et al*, 2014).

Body composition changes may add to increased frailty, poor mobility and disability (Narici & Maffulli, 2010; Miceli *et al*, 2011; Morgan *et al*, 2013). ‘Sarcopenic obesity’, reflecting loss of muscle mass with an increase in fat, has been reported in a high proportion of intensively treated myeloma patients (Greenfield *et al*, 2014), which contrasts with the picture in other advanced cancers characterised by cachexia.

Guideline

Proposed causes include endocrine, metabolic and nutritional factors and reduced physical activity (Morley *et al*, 2001; Newman *et al*, 2003; Locatelli *et al*, 2004; Saunders *et al*, 2014), along with myeloma itself, also classically associated with progressive loss of height. Routine measurements of weight or body mass index (BMI) are poor proxies for assessment of body composition, although accurate assessment [e.g. by dual-energy X-ray absorptiometry (DEXA) scanning] is less accessible.

Recommendations

Assessment.

- Offer annual screening for endocrine disorders, for hypothyroidism, hypogonadism in males, and younger female patients for menopausal symptoms particularly following intensive (HSCT-based) treatments (Grade 2B).
- Assess weight, height, body mass index (BMI), waist circumference, strength and frailty regularly, and blood pressure, HbA_{1c} and full lipid profile annually, and refer to primary care for follow-up as appropriate (Grade 2B).

Management.

- Reduce bone risk with weight-bearing exercise, bisphosphonates, calcium/vitamin D supplementation and dietary advice (Grade 1B).
- Offer hormone replacement in both female and male patients where appropriate, with specialist advice (Grade 2B).

Neurological and eye complications

Spinal cord or nerve root compression is the most common neurological complication of newly presenting or relapsing myeloma. Chemotherapy-induced peripheral neuropathy (CIPN) is the most common neurological complication in long-term survivors, and has both peripheral and central nervous system (processing) components (Boland *et al*, 2014a). Polyneuropathy may also be a feature of myeloma, amyloidosis and POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes) syndrome at presentation, and/or related to comorbidities such as diabetes mellitus, carpal tunnel and other nerve compression syndromes, CKD and vitamin deficiency.

Management of peripheral neuropathy (PN) is summarised in the BCSH Guidelines in Supportive Care in Myeloma (Snowden *et al*, 2011). Apart from dose or schedule adjustment, treatment for CIPN remains symptom-directed. Symptoms resolve or improve in most patients, but some are left with permanent disability. Neurotoxic drug treatments should be used with caution in patients with PN from any

cause. Additional investigations to identify potential causes are warranted.

The advancing age of the myeloma population and intermittent but high-dose corticosteroid usage are risk factors for cataract formation, although incidence in the myeloma population is unknown. Total body irradiation (TBI) is rare in current myeloma practice, but even in transplant patients who do not receive TBI, the incidence of cataracts may be as high as 5–20% at 10 years (Schutt *et al*, 2006). Risks of diabetic eye disease may be increased in myeloma patients by high-dose corticosteroids.

Recommendations

Assessment.

- Screen all patients with peripheral neuropathy (PN) with thyroid function tests, vitamin B12, diabetes and renal compromise (Grade 2C).
- Offer a specialist neurology assessment in patients with Grade II-IV PN (Grade 2C).
- Consider annual ophthalmic screening for cataract and other ocular problems. (Grade 2C).

Management.

- Reduce or eliminate neurotoxic agents in chemotherapy-induced peripheral neuropathy (CIPN) and offer gabapentin or pregabalin for long-term symptom control (Grade 1B).
- Consider referral to a pain specialist (Grade 2C).

Cardiovascular and respiratory complications

Clinical and sub-clinical cardiovascular and respiratory abnormalities occur at a high prevalence in intensively treated myeloma survivors. Abnormalities of electrocardiography, echocardiography, natriuretic peptide levels and pulmonary function testing are seen in around half of patients and are associated with reduced HRQoL (Foley *et al*, 2010; Kozelj *et al*, 2013; Samuelson *et al*, 2016).

Impaired respiratory function results from recurrent or persistent upper and lower airway infections, thromboembolism and chemotherapy and radiation exposure, as well as from common causes such as smoking (Mankikian *et al*, 2014). Ventilatory function may be affected by pain and fractures due to spinal and chest wall bone disease, as well as opiate analgesia.

Sodium- and fluid-retaining effects of corticosteroids and IMIDs may add to cardiac problems, and cardiac amyloid should always be considered, especially with right-sided heart failure. Anaemia may cause cardiovascular and respiratory symptoms, as may a high BMI, and may respond to transfusion, ESAs and weight loss (Boland *et al*, 2013; Pratt *et al*, 2014; Samuelson *et al*, 2016).

Risk factors for cardiovascular disease (obesity, hypertension, hyperlipidaemia and hyperinsulinaemia) are common in myeloma patients. The metabolic syndrome, a complex of truncal obesity, hypertension, hyperlipidaemia, insulin resistance and type II diabetes mellitus, exists in as many as 50% of patients following HSCT (DeFilipp *et al*, 2016).

Given the extended life expectancy as a result of modern treatments, routine screening and lifestyle modification combined with primary and secondary preventive strategies are more justified to reduce cardiovascular disease. Dietary weight management (in overweight and obese patients) and smoking cessation should be encouraged. Physical activity, especially after HSCT, may be beneficial for both physical and psychological functioning in myeloma patients (Dimeo *et al*, 1997; Coleman *et al*, 2003). Physical activity should ideally be supervised, tailored and form part of rehabilitation programmes.

As well as lifestyle modification, there is also a case for cardiovascular and respiratory screening for risk factors, for sub-clinical disease and in patients with symptoms, such as breathlessness and oedema, which could be attributed to other causes. Natriuretic peptide testing can be used as a 'rule out' test to select patients who need priority referral for echocardiography (Cowie *et al*, 2010). Although raised plasma B-type Natriuretic peptide (BNP) or N-Terminal pro-B-type natriuretic peptide (NT-BNP) levels do not diagnose heart failure, they have a high negative predictive value: and other causes for symptoms should be determined. A serum BNP level less than 100 pg/ml (29 pmol/l) or an NT-BNP level less than 400 pg/ml (47 pmol/l) in an untreated patient makes a diagnosis of heart failure unlikely. Patients with a BNP level above 100 pg/ml or an NT-BNP level above 400 pg/ml should have echocardiography and specialist assessment. Further guidance is provided by NICE (2010).

Recommendations

Assessment.

- Offer routine screening for cardiovascular risk (Grade 2C).
- Check natriuretic peptide (BNP or NT-BNP) with annual screening or when clinically indicated (Grade 2C).
- Consider electrocardiogram, echocardiography and pulmonary function testing in patients at risk (including abnormal natriuretic peptide levels) or when clinically indicated (Grade 2C).

Management.

- Offer counselling for lifestyle modification, including diet, weight control, smoking cessation and appropriate physical activity (Grade 2C).
- Consider referral to specialist for patients with established cardiac and respiratory disease (Grade 2C).

- Consider ESAs or blood transfusion for symptomatic anaemia (Grade 1B).

Oral and dental hygiene

Maintenance of oral and dental hygiene is relevant to all myeloma patients, whether or not they have undergone HSCT (Schutt *et al*, 2006; Snowden *et al*, 2011; Pratt *et al*, 2014). Regular dental review will not only help identify the risk of bisphosphonate-related osteonecrosis of the jaw (BRONJ), but should also cover a broader range of issues. Oral dryness is a common side effect of chemotherapy, radiotherapy and some supportive care drugs. Dryness and decreased salivation may lead to dental problems and infections. Patients may complain of discomfort and hypersensitivity, taste disturbances, soreness of the throat (including oral candidiasis), and/or problems in speaking and swallowing. Oral cancers may be increased in patients following HSCT and IMiD usage.

Recommendations

Assessment.

- Encourage annual dental review and maintenance of oral and dental hygiene (Grade 2C).
- Monitor patients needing dental surgery for bisphosphonate-related osteonecrosis of the jaw (BRONJ) (Grade 2C).
- Investigate non-healing lesions and consider specialist referral (Grade 2C).

Management.

- Recommend rinses and other treatments, e.g. artificial saliva to treat oral dryness and other symptoms (Grade 2C).

Gastroenterological and nutritional problems

Bowel disturbance, particularly diarrhoea, is a common and sometimes persistent side effect of treatment with novel agents, such as bortezomib, and histone deacetylase inhibitors, such as panobinostat. Diarrhoea also occurs with lenalidomide; it is probably due to bile acid malabsorption and responds to bile acid sequestrants (Pawlyn *et al*, 2014). Patients with persistent diarrhoea with no obvious infectious aetiology need referral to a gastroenterologist to exclude malignancy, underlying bowel disease, AL amyloidosis and bile acid malabsorption. Constipation is common in myeloma patients and may be the result of side effects of thalidomide, opioids, anticholinergics or 5-HT3 receptor antagonists, or hypercalcaemia. Laxative treatment is commonly used; a combination of a stool softener with a stimulant.

Guideline

Ongoing nausea and emesis may occur due to anti-myeloma therapy, analgesics, renal failure and hypercalcaemia. Anorexia is common during HSCT, when significant weight loss and nutritional deficiencies can occur (Murray & Pindoria, 2009; Iversen *et al*, 2010). Correctable nutritional deficiencies may be due to poor appetite, sub-optimal diet and insufficient exposure to sunlight. In common with the general population (Greenfield *et al*, 2014), a substantial proportion of patients have evidence of vitamin D insufficiency, potentially compounding myeloma bone disease, fatigue and other symptoms (Diamond *et al*, 2010; Greenfield *et al*, 2014; Maier *et al*, 2015). Folate deficiency and reduced vitamin B12 levels are relatively common although serum paraproteins may interfere with vitamin B12 measurement (Greenfield *et al*, 2014; Wongrakpanich *et al*, 2015). Iron deficiency is rare but raised serum ferritin levels, which appear to be relatively common in patients with advanced myeloma, are likely to be multifactorial in origin. Diagnosis of iron overload therefore requires more specialised investigation (Greenfield *et al*, 2014).

Abnormal liver function tests may be caused by a variety of causes, including drugs, infections and lifestyle factors, including alcohol consumption (Boland *et al*, 2013).

Recommendations

Assessment.

- Routinely monitor weight, dietary intake and upper and lower gastrointestinal (GI) symptoms (Grade 2C).
- Routinely assess liver function tests, drug and alcohol history (Grade 2C).
- Consider screening annually for vitamin D, B12, folate and ferritin levels (Grade 2C).

Management.

- Correct nutritional deficiencies (Grade 2C).
- Consider referral to a dietician in patients losing weight (Grade 2C).
- Consider referring patients with unexplained weight loss, altered bowel habit or abnormal liver function tests for specialist assessment (Grade 2C).

Second primary malignancies

An increase in therapy-related myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) in patients with myeloma was first recognised several decades ago and again more recently in patients on lenalidomide maintenance therapy. The risk of developing MDS or AML is increased 8- to 11-fold compared to the general population (Barlogie *et al*, 2008; Mailankody *et al*, 2011; Matarraz *et al*, 2012; Thomas *et al*, 2012; Roeker *et al*, 2013) particularly with prolonged exposure to alkylating agents, most notably melphalan (Kyle

et al, 1970; Bergsagel *et al*, 1979; Greene *et al*, 1986; Cuzick *et al*, 1987; Finnish Leukaemia Group, 2000).

Three large randomised trials of lenalidomide maintenance have all shown a small excess of second primary malignancies (SPMs) in lenalidomide-treated patients compared to the placebo-treated patients [Intergroupe Francophone du Myélome (IFM) 2005–2002 (Attal *et al*, 2012), Cancer and Leukemia Group B (CALGB) 100104 (McCarthy *et al*, 2012), and Multiple myeloma (MM)-015 (Palumbo *et al*, 2012)]. Other reports have supported an incidence for SPMs of up to 6.9% (Dimopoulos *et al*, 2011; Srivastava *et al*, 2013; Palumbo *et al*, 2014). However Thomas *et al* (2012) highlighted the limitations of current studies. The risk of secondary AML/MDS for patients with myeloma remains low and is far outweighed by the current risk of toxicity and death from myeloma. The relative risk of myeloma patients developing solid tumours appears less than that for therapy-related AML/MDS, and may not be significantly above that of the general population. However, it is likely that SPMs will increase in patients with myeloma simply due to the increasing survival of this ageing population.

Recommendations

Assessment.

- Consider acute myeloid leukaemia/myelodysplastic syndrome (AML/MDS) as a potential diagnosis in patients with persistent or worsening cytopenias (Grade 2C).
- Encourage vigilance for other malignancies and investigate suspicious symptoms promptly (Grade 2C).

Management.

- Encourage participation in routine NHS cancer screening (Grade 2C).
- Develop a system for formal recording of second primary malignancies and ongoing investigation for any possible links with treatment (Grade 2C).

Part 2. Frailty, psychosocial and rehabilitation considerations

Elderly and frail patients

Myeloma has a median age of >70 years at diagnosis (<http://seer.cancer.gov/statfacts/html/mulmy.html>). Survival is reduced and toxicities increased in older patients (Bringhen *et al*, 2013; Wildes *et al*, 2014; Palumbo *et al*, 2015), and therefore assessing the impact of ageing processes on a patient is crucial in optimising outcomes. As people age they become increasingly vulnerable to external stressors, such as infection, through a combination of frailty, disability and comorbidity (Table III). The aim of assessment is threefold; to predict toxicity and hence modify planned treatment,

provide prognostic information, and to detect disability (which may be supported). Older patients often choose HRQoL over overall survival (Yellen *et al*, 1994; Fried *et al*, 2002) and need the opportunity to make informed decisions about treatment.

Geriatic assessment

A Comprehensive Geriatric Assessment (CGA) is a multidimensional, interdisciplinary diagnostic process focusing on determining an older person's medical, psychosocial and functional capabilities to develop a coordinated plan for treatment and long-term follow-up (Rubenstein *et al*, 1991). Geriatric assessment (GA) refers to an abbreviated assessment using a range of different shortened tools. No one tool has been shown to be better than another in oncology (Wildiers *et al*, 2014) and different tools emphasise different domains. None are as sensitive as a CGA (Hamaker *et al*, 2012).

Retrospective studies show inferior outcomes in patients who experience toxicities and treatment discontinuations (Wildes *et al*, 2014). These 'at risk' patients need to be identified prospectively and treatment modified (via dose reduction or regimen modification). GA can identify age-related problems missed by a routine history and physical examination in approximately half of patients (Caillet *et al*, 2011) and performance status underestimates the degree of disability (Extermann *et al*, 1998; Repetto *et al*, 2002). Although using a formal assessment tool *versus* a standard history and examination in terms of final outcomes and identifying the most meaningful vulnerabilities is yet to be tested prospectively, a systematic method can facilitate identification and correction of a disability. Ideally, assessment and onward referral should be done in collaboration with a

multidisciplinary team including elderly care medicine, nurses and therapists as well as communicating with the GP, social care, and third sector services.

A simple frailty score in myeloma includes age, comorbidities and GA. It correlates well with risk of severe toxicity (Palumbo *et al*, 2015). The score is simple to use, especially in the electronic format available, but may lack discriminatory power for the very frail because it was based on a trial population, of which only 2% had a performance status of 3–4. Application of this score system is expected to be used increasingly in trials and may prove useful in the clinic. As this frailty index found age >75 years to be a risk factor for increased mortality and toxicity, a reasonable minimum is to assess all patients aged ≥75 years and any others with a suggestion of frailty.

Recommendations

Assessment.

- Consider a baseline geriatric assessment in elderly and frail patients, particularly those aged ≥75 years (Grade 2C).
- Consider using the outcome of an assessment to guide treatment choice and prognosis (Grade 2C).

Management.

- Engage with elderly care teams to provide geriatric assessment, optimised care plans and to make joint onward referrals when disabilities are identified (Grade 2C).

Assessment of patient concerns and information provision

As well as physical issues, psychological problems, social factors and concern about treatments and maintaining independence, all have a significant impact on HRQoL (Frodin *et al*, 2010; Molassiotis *et al*, 2011a,b). After 1 year of follow-up, 75% of myeloma patients have deteriorating HRQoL scores, with 37% worrying about their future health, 34% preoccupied by their disease and 21% worrying about dying (Mols *et al*, 2012). Most HRQoL tools [such as the European Organisation for Research and Treatment of Cancer Quality of Life (EORTC) QLQ-C30 and MY-20 questionnaires] are used in clinical research rather than in routine clinical practice (Kvam *et al*, 2009; Osborne *et al*, 2012). However, the Myeloma Patient Outcome Scale (MyPOS) HRQoL questionnaire has been designed specifically for use in the clinical setting and focuses on the issues most important to patients (Osborne *et al*, 2012, 2015).

The importance of using structured holistic needs assessments (HNA) at key stages of cancer from diagnosis is now recognised (Department of Health, Macmillan Cancer Support and NHS Improvement, 2013). The Recovery Package

Table III. Frailty, disability and co-morbidity.

Concept	Definition
Frailty	A phenotype (≥ 3 of weakness, poor endurance, weight loss, low physical activity and slow gait speed (Fried <i>et al</i> , 2001) <i>or</i> as the cumulative effect of individual deficits – 'the more individuals have wrong with them, the more likely they are to be frail' (Rockwood & Mitnitski, 2007)
Disability	Difficulty or dependency in carrying out activities essential to independent living including tasks needed for self-care and living independently in a home, and desired activities important to one's quality of life (Fried <i>et al</i> , 2004)
Comorbidity	Concurrent presence of ≥ 2 medically diagnosed diseases in the same person, with the diagnosis of each contributing disease based on established, widely recognised criteria (Fried <i>et al</i> , 2004)

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(Cancer Research UK 2015) recommends the use of a HNA to identify the individual needs of the person affected by cancer at key points in the care pathway and if health and social needs change; ensuring that care is responsive to changing needs, and support services are planned and accessed appropriately (Richards *et al*, 2011a).

The aim of an HNA is to comprehensively assess physical, emotional, mental, spiritual and social concerns experienced by the individual and to formulate an individual care or action plan (Richardson *et al*, 2007). Several HNA tools are available, for example the Sheffield Profile for Assessment and Referral for Care (SPARC) questionnaire (Ahmed *et al* 2014). A recent cross-sectional study used the SPARC tool in a group of patients with advanced, multiply relapsed and heavily pre-treated but stable myeloma. The patients had a high symptom burden, were bothered and distressed by the side effects and long-term effects of treatments, and were worried about the effect their disease was having on their family or other people (Boland *et al*, 2014b).

Recommendations

Assessment.

- Consider routine holistic needs assessments (HNA) at the start and end of each line of treatment to identify individual patient needs and concerns (Grade 2C).

Management.

- Plan provision of support services accordingly (Grade 2C).
- Provide information on the late effects of potential treatments and advise patients on strategies to reduce risk and manage treatment side effects (Grade 2C).

Psychological wellbeing

Myeloma patients are concerned by disease recurrence, loss of independence, and death. However, overall mental functioning remains preserved, suggesting effective coping mechanisms (Boland *et al*, 2013). In a survey of 114 patients, anxiety (8%) and depression (24%) were reported at the time of myeloma diagnosis and 51% of these patients had psychosocial intervention desires. The most common preferences were relaxation techniques, psychological counselling and peer support groups (Lamers *et al*, 2013). Cognitive impairment, pre-transplantation, has also been recognised leading to accentuated problems post-transplantation: mainly deficits in learning/memory, executive function, motor function and psychomotor speed (Jones *et al*, 2013).

Low mood, anxiety and clinical depression should be actively assessed and managed. A four-level model of psychological assessment and support is recommended by

NICE to guide escalation of professional intervention (NICE 2004). Alongside this, support groups and resources provided by cancer support organisations may reduce isolation and build sustainable support networks outside the hospital setting.

Recommendations

Assessment.

- Regularly assess patient mood, anxiety and cognitive status through holistic needs assessments (HNA), patient presentation or concern, at least at the start and end of each line of treatment, or annually (Grade 2C).

Management.

- Escalate to psychological care or psychiatrist if clinically appropriate (Grade 2C).
- Alert patients to support resources and groups outside the hospital setting (Grade 2C).

Table IV. Recommendations for core attendance of multidisciplinary team (MDT) members responsible for the care of patients following completion of treatment.

Late effects core team	Late effects MDT associate membership	Social care and voluntary services
Lead clinician (haematologist with expertise in late effects)	General practitioner (individual basis)	Social worker
Clinical nurse specialist	Geriatrician	Patient support group
Physiotherapist	Liaison psychiatrist	Cancer information services
Psychologist	Endocrinologist and metabolic bone physician	Citizens advice
Occupational therapist	Cardiologist	Elderly/cancer charities
	Immunologist	Guidance with complementary therapy if patient expresses interest
	Renal physician	
	Gastroenterologist	
	Respiratory physician	
	Neurologist	
	Ophthalmologist	
	Dermatologist	
	Psychosexual oncology counsellor	
	Supportive/palliative care consultant	

Table V. Recommendations for timing and frequency of assessment of late and long-term consequences of myeloma and its treatment: long-term physical consequences.

Issue	Assessment	Timing and frequency
Overall condition	Full physical examination Weight maintenance Height Blood pressure Urinalysis HNA Systems review Drug interaction check Patient education, including awareness of early signs of infection and need to seek medical attention without delay Appraisal of vaccination record, whether transplanted or not Influenza vaccine Monitoring of renal function	Annually as a minimum Each clinic visit Annually without shoes – blunt indication of possible vertebral collapse Annually as a minimum Annually as a minimum After each treatment episode and then annually Annually To be made by a pharmacist at every treatment change Annually, including update of unit self-referral policy for suspected infection in immunocompromised patients whether on or off chemotherapy Annually
Infection and immunity	Patient education, including awareness of early signs of infection and need to seek medical attention without delay Appraisal of vaccination record, whether transplanted or not Influenza vaccine Monitoring of renal function	Annually in season At every clinic visit or at least every 3 months, refer for specialist advice if persistent stage 2 CKD or greater
Renal and urogenital conditions	Monitoring levels of vitamin D, calcium	Annually
Bone and endocrine disorders	Screening for hypogonadism in males	Annual serum morning testosterone, sex-hormone-binding globulin and gonadotrophins in patients post-HSCT or if symptomatic
	Screening for menopausal symptoms in females <50 years of age	Take menopausal history and screen younger females for menopausal symptoms with serum oestradiol and gonadotrophins
Neurological and ocular complications	Monitoring of thyroid function Screening for metabolic causes of peripheral neuropathy: thyroid function, vitamin B12 levels and diabetes Identification of patients with persistent Grade II-IV peripheral neuropathy Screening for visual acuity, cataract and other ocular problems	Annually or if symptomatic In all patients with peripheral neuropathy on presentation
	Monitoring for acute myeloid leukaemia/ myelodysplastic syndrome in patients with persistent or worsening cytopenias	As needed – refer to neurology for specialised assessment
Second primary malignancies	Monitoring for non-healing oral lesions and other malignancies Obesity/BMI/waist circumference/blood pressure	Annual eye check by opticians unless specific problems merit referral to ophthalmology Full blood count each visit or urgently on presentation of suspicious signs and symptoms
Cardiovascular and respiratory complications	Assess risk factors for metabolic syndrome and educate patient and GP on increased risks Non-fasting blood glucose and HbA _{1c} and lipid profile Patient and GP education on increased risks, and need for extra vigilance Refer to smoking cessation services Physical activity and exercise, local provision such as health walks BNP or NT-BNP Echocardiography/ECG Pulmonary function tests	Patient education regarding regular dental checks and urgent referral to specialist services if clinically indicated At diagnosis and annually
Oral and dental hygiene	Monitoring for BRONJ, oral cancer, candidiasis	Annually, unless already on statin or primary care management for diabetes mellitus or hyperlipidaemia At annual review As needed As needed
		Annually and as clinically indicated In patients at risk and repeat as clinically indicated In patients at risk and repeat as clinically indicated At diagnosis and at a change in condition

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Table V. (Continued)

Issue	Assessment	Timing and frequency
Gastroenterological problems and nutrition	Screening for iron overload	At diagnosis and annually in patients who have had blood transfusions
	Monitoring of vitamin D, folate, B12 and ferritin level	At diagnosis, and annually and as clinically indicated
	Refer to alcohol advisory services via GP	As needed
Elderly and frail patients	Consider geriatric assessment in elderly and frail patients, particularly those aged >75 years	At baseline
Psychological wellbeing	Consider routine HNA to identify individual patient needs and concerns	At the start and end of each line of treatment, or annually
	Mental health and wellbeing (mood/anxiety/clinical depression) – assessment through HNA, patient presentation or concern	At the start and end of each line of treatment, or annually, with escalation to more specialist support as indicated
Pain	Consider routine HNA to identify individual patient needs and concerns	At the start and end of each line of treatment, or annually and at a change in condition
Fatigue	Consider routine HNA to identify individual patient needs and concerns	At the start and end of each line of treatment, or annually and at a change in condition
Prehabilitation and rehabilitation	Ensure that prehabilitation and rehabilitation are an integral part of every line of treatment in the patient care pathway Encourage regular physical activity starting from time of diagnosis and address patient concerns Encourage continual aspiration to a generally healthy lifestyle (i.e. not related to myeloma treatment), including regular exercise	At diagnosis, at start and end of line of treatment and at a change in condition
Impact on work ability	Consider routine HNA to identify individual patient needs and concerns	At the start and end of each line of treatment, or annually

BMI, body mass index; BNP, B-type natriuretic peptide; BRONJ, bisphosphonate-related osteonecrosis of the jaw; CKD, chronic kidney disease; ECG, electrocardiogram; GP, general practitioner; HNA, holistic needs assessment; HSCT, haematopoietic stem cell transplantation; NT-BNP, N-Terminal pro B-type natriuretic peptide.

Pain and fatigue

Myeloma patients have the highest level of symptoms and the lowest level of HRQoL among patients with haematological cancers (Johnsen *et al*, 2009). The influence of fatigue and pain are the strongest predictors on HRQoL in myeloma (Jordan *et al*, 2014) and these long-term consequences of treatment are known to be the main barriers to social and participatory functions, even in stable phase disease (Gulbrandsen *et al*, 2004; Boland *et al*, 2013; Jordan *et al*, 2014).

A recent European multi-centre study of myeloma patients reported that depression and fatigue had a negative effect on HRQoL; fatigue and bone pain were associated with poor physical functioning whilst mental status changes were associated with a reduction in social functioning score (Jordan *et al*, 2014).

Fatigue occurs in the majority of myeloma patients and it is usually multi-factorial. Common treatable causes include anaemia, biochemical and endocrine abnormalities and use of sedating medication and other medicines, such as

corticosteroids, anti-arrhythmics, anti-hypertensives, strong analgesics and chemotherapy. When assessing fatigue, it is vital to ask for key components such as duration, and impact of rest and impact on physical and mental activity and sleep activity (<http://us.bestpractice.bmjjournals.com/best-practice/monograph/571.html>; accessed 9 February 2016). Exercise and physical activity may help; in a single arm pilot study, a tailored exercise programme was associated with increased muscle strength and improved fatigue scores (Groeneveldt *et al*, 2013). However, high quality trials are lacking, and existing evidence suggests that positive impacts on fatigue may be limited to the post-treatment period (Smith *et al*, 2015; Gan *et al*, 2016). Consideration should be given to referral to rehabilitation services. In extreme cases a trial of a central nervous system stimulant may be justified, but this must be delivered under specialist advice.

Detailed information is given on the assessment and management of pain in published BCSH guidelines (Pratt *et al*, 2014).

Table VI. Comparison of these British Society for Haematology (BSH) Guidelines and other international survivorship guidelines in myeloma.

BSH Guidelines for Screening and Management of Late and Long-term Consequences of Myeloma and its Treatments	US Nurse Leadership Board guidelines (Bertolotti <i>et al</i> , 2008; Faiman <i>et al</i> , 2008; Smith <i>et al</i> , 2008; Bilotti <i>et al</i> , 2011a,b; Richards <i>et al</i> , 2011b)
Multi-disciplinary writing group, including consumer representation, with professional sounding board review	Nursing-led guidelines for multidisciplinary dissemination
Emphasis on long-term disease complications and late effects of treatment along with consideration of global issues, such as frailty and geriatric assessment	Emphasis on key aspects of survivorship – health maintenance, bone, renal, sexual dysfunction, mobility, as well as toxicity of novel agents
Combined medical systems and psychosocial model	Topics considered to have most impact on patient survivorship
One integrated guideline document, with systematic literature review and recommendations	Several guideline documents with recommendations for specific areas of practice

Recommendations

Pain

Assessment

- Consider routine holistic needs assessment (HNA) to identify individual patient needs and concerns (Grade 2C).
- Take detailed history of pain using a 0–10 numerical scale, body chart and pain inventory and its impact (Grade 2B).
- Assess mental health status (Grade 2B).
- Ensure follow-up assessment as routine practice (Grade 2B).

Management

- Follow existing guidelines for management of pain (Grade 2C).

Fatigue

Assessment

- Consider routine HNA to identify individual patient needs and concerns (Grade 2C).
- Take detailed history of energy levels and fatigue, and rule out possible causes of fatigue, including low mood (Grade 2C).

Management

- Consider exercise, physical activity and rehabilitation services (Grade 2C).
- Treat organic causes of fatigue, or in extreme cases, refer to generic chronic fatigue services. Where low mood is a factor, refer for counselling or psychological intervention (Grade 2C).

Physical fitness and functionality

Only 20% of myeloma patients meet national physical activity guidelines post-treatment and 7% during active treatment (Jones *et al*, 2004; Craike *et al*, 2013). Commonly reported barriers to physical activity are pain, fear of fracture risk, lack of confidence and fatigue (Groeneveldt *et al*, 2013). Although more high quality randomised control trials (RCTs) are required in myeloma patients to determine efficacy (Gan *et al*, 2016; Smith *et al*, 2015), exercise training has been shown to be safe and feasible (Groeneveldt *et al*, 2013), with high attendance and adherence (Groeneveldt *et al*, 2013; Shallwani *et al*, 2015) and higher physical activity levels have been associated with better quality of life both during and off active treatment (Jones *et al*, 2004; Groeneveldt *et al*, 2013). Rehabilitation in myeloma patients after HSCT improves physical performance, muscle strength, aerobic capacity and immunological function; reduces fatigue and improves psychological outcomes (Groeneveldt *et al*, 2013; Persoon *et al*, 2013).

Prehabilitation has the potential to improve outcomes for this group of patients (Silver & Baima, 2013; Bartels *et al*, 2015) and should be considered prior to the start of treatment, in order to minimise functional decline and loss of physical fitness during chemotherapy. Evidence for the benefit of prehabilitation programmes in other cancer survivors is growing (Gillis *et al*, 2014).

Recommendations

Management

- Ensure that prehabilitation and rehabilitation are an integral part of every line of treatment in the patient care pathway (Grade 2C).
- Encourage regular physical activity starting from time of diagnosis and address patient concerns (Grade 2C).
- Encourage continual aspiration to a generally healthy lifestyle (i.e. not related to myeloma treatment), including regular exercise (Grade 2C).

Implications for work ability

Work productivity loss through cancer has significant economic consequences for individuals, their families and society (Luengo-Fernandez *et al*, 2013). More than this, the ability to work maintains financial stability, social

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relationships, self-esteem and psychological well-being (Goodwin *et al*, 2013; Horsboel *et al*, 2013; Timmons *et al*, 2013; Wells *et al*, 2013). Two-thirds of patients with haematological malignancies return to work. However, the proportion is lowest for myeloma and acute leukaemia patients. While myeloma mainly affects older people who are closer to retirement, the relatively high symptom burden and associated drugs may also be significant. Healthcare professionals can have a key influence on the likelihood of the patient's subsequent return to work (Pryce *et al*, 2007) and should take opportunities to assess the impact of disease and treatment consequences have on a person's ability to maintain their working life, and as a result, their identity and financial security (Wells *et al*, 2014).

Recommendations

Assessment.

- Consider routine holistic needs assessment (HNA) to identify individual patient needs and concerns (Grade 2C).
- Signpost patients to relevant services (Grade 2C).
- Ensure careful communication between the specialist team, GP and patient on suitable timing for return to work, if appropriate (Grade 2C).

Conclusions: living with myeloma

We are entering a watershed period in which patients are expecting to live in excess of 5–10 years after a diagnosis of myeloma and issues of survivorship are becoming increasingly important. Although care of myeloma patients is traditionally based around secondary care, primary care professionals need to be empowered to manage the consequences of the disease and its treatment.

Analyses may be drawn from more developed examples of comprehensive care in other chronic but incurable diseases, such as diabetes, where both secondary and primary

care work closely together with well developed input from specialist nurses. As myeloma is a relatively rare disease state, additional training of the healthcare workforce may be indicated and communication between the secondary specialist care team and primary care is paramount. To equip patients to manage the late effects of myeloma, information on social and financial issues, return to work, travel, immunisations, relationships and sexual function, and psychological support is particularly important, as well as awareness of general health promotion strategies and routine health screening. Patients and families should have clear information on which health and social care team to contact if they have concerns.

Recommended partners in the multidisciplinary core and supporting teams for assessment and treatment of myeloma late effects are summarised in Table IV. Table V indicates the recommended timing and frequency for screening and assessment schedules. Table VI compares these BSH guidelines with previously published survivorship guidelines in myeloma. Although the evidence base is currently limited, these guidelines and recommendations provide a framework for clinicians to optimise management of long-term complications as an important component of comprehensive care of myeloma as well as future areas for research and development.

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Appendix

GRADE: Grading of Recommendations Assessment, Development and Evaluation

Strength of recommendations

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

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

Quality of evidence

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

Guideline

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

(B) Moderate. Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g. inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g. lack of blinding, large losses to

follow up, failure to adhere to intention to treat analysis) or very strong evidence from observational studies or case series (e.g. large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

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