

High prevalence of cardiovascular and respiratory abnormalities in advanced, intensively treated (transplanted) myeloma: The case for ‘late effects’ screening and preventive strategies

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Objectives: Modern management of myeloma has significantly improved survival, with increasing numbers of patients living beyond a decade. However, little is known about the long-term cardiovascular and respiratory status of intensively treated and multiply relapsed survivors.

Methods: We performed detailed cardiovascular and respiratory evaluations in patients with intensively treated, advanced but stable myeloma. All patients had received at least two lines of treatment, including at least one haematopoietic stem cell transplantation procedure, but had stable, controlled disease and were off active treatment at the time of evaluation.

Results: Thirty-two patients with a median duration of 6 years (range 2–12) from original diagnosis of myeloma and three lines (range 2–6) of treatment were evaluated. Despite normal physical examination in the majority, there was a high prevalence of sub-clinical cardiac and respiratory dysfunction, reflected by abnormalities of electrocardiography (45%), echocardiography (50%), serum N-terminal pro-B-type natriuretic peptide level (NT-pro-BNP, 50%), and pulmonary function testing (45%). NT-pro-BNP level correlated negatively with quality of life ($P=0.012$) and positively with serum ferritin ($P=0.027$). Dyspnoea score correlated with BMI ($P=0.001$). Risk factors for cardiovascular disease (obesity, hypertension, hyperlipidaemia, and hyperinsulinaemia) were common.

Discussion: Even in the absence of overt clinical features, the majority of intensively treated long-term survivors of myeloma have established cardiovascular and/or respiratory dysfunction, above levels expected in the general population of a similar age.

Conclusion: This study supports routine screening and lifestyle modification combined with primary and secondary preventive strategies to reduce cardiovascular and respiratory disease and to preserve quality of life in transplanted myeloma patients.

Keywords: Myeloma, Stem cell transplantation, Late effects, Cardiovascular, Respiratory

Introduction

The life expectancy of patients with myeloma has increased significantly over the last decade. Although the vast majority of patients remain incurable, disease control is possible with an increasing array of novel agents along with improved supportive care measures, and many patients now live beyond a decade with their disease.^{1,2} In addition to the direct

effects of the disease, exposure to multiple anti-myeloma agents is associated with an accumulation of side effects affecting many organ systems. Whilst some may be reversible and short lived, others are insidious in onset, and result in permanent damage or ‘late effects’.

‘Late effects’ is perhaps best defined as per the NCI definition as ‘A health problem that occurs 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

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social problems and second cancers'. In myeloma, such 'late effects' may be additive or synergistic with other cytotoxic and supportive agents, and with organ damage caused by myeloma or other processes such as the degenerative conditions commonly experienced by an ageing population.^{3,4} Patients with myeloma are progressively compromised due to a complex set of complications related to myeloma, its treatment, and advancing age.⁵

Although 'late effects' screening practices have been recommended following haematopoietic stem cell transplantation (HSCT),⁶ and many patients with myeloma have HSCT, the situation is arguably more complex than for many other HSCT indications as myeloma is a multisystem disease; transplant procedures are not usually curative (with relapse being common after many allogeneic procedures) and patients typically have several lines of anti-myeloma treatment in a lifetime (including more than one transplant procedure).

The previously limited prognosis of myeloma combined with the long-term horizon of cardiovascular risk factors have meant that screening, modification and treatment were not a priority and perhaps difficult to justify. The improving prognosis combined with increasing recognition that intensive cytotoxic therapy and HSCT are associated with 'late' cardiovascular and respiratory effects may mean more active screening and treatment of cardiovascular risk factors is warranted.^{4,7-9} However, data remain scarce.

The aim of this exploratory study was to characterize the cardiovascular and respiratory status of a cohort of patients with intensively treated (i.e. transplanted), multiply relapsed but stable myeloma. Such information would be useful in designing models for comprehensive care in myeloma, aimed at maintaining general health and quality of life in long-term survivors.

Patients and methods

Design and eligibility – including consideration of human rights

This cross-sectional observational study was conducted in compliance with the EU GCP directive and approved by Sheffield Teaching Hospitals NHS Foundation Trust R&D Department following local Research Ethics Committee review.¹⁰ Inclusion criteria included diagnosis of 'symptomatic myeloma' by International Working Group criteria,¹ a history of initial treatment with induction therapy consolidated by at least one HSCT procedure, followed by at least one additional line of treatment for progressive or relapsed disease. In order to eliminate the effects of active myeloma and its treatment, only patients with controlled disease, i.e. paraprotein plateau/non-progressive phase off active treatment or on maintenance

treatments for at least 3 months, were recruited. Exclusion criteria included uncontrolled disease and inability to give informed consent.

Assessments

Standardized data collection forms were used to obtain information relating to previous management of myeloma and all co-morbidities, based on medical records and standardized patient history. Standardized physical examinations of the cardiovascular and respiratory systems were performed by experienced (i.e. MRCP (UK) qualified) physicians.

Electrocardiography (ECG) was performed according to standard protocols and electrocardiograms were reviewed in a blinded fashion by a single consultant cardiologist (EU specialist register). Echocardiography was performed by sonographers trained to UK national accreditation standards and echocardiograms were reported by the reviewing echocardiographer according to British Society of Echocardiography criteria.¹¹ Serum N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) was measured and values above 15 pmol/l (125 pg/ml) were considered to be significantly raised in accordance with published criteria for this age group.¹²

Spirometry was performed using a Viasys Microlab spirometer, according to manufacturer's instructions. A restrictive picture was defined as FVC (forced vital capacity) <80% of predicted with an FEV1 (forced expiratory volume in 1 second)/FVC ratio >80%; an obstructive picture defined as FEV1/FVC ratio <70% with FVC >80% predicted and mixed picture defined as FVC <80% predicted and FEV1/FVC <80%. Spirometry was considered normal if not meeting any of above criteria.¹³ Maximal expiratory (MEP) and inspiratory (MIP) pressures were measured, with lower limits of normal for individual patients calculated using previously published formulae.¹⁴

Body mass index (BMI) and nutritional status were assessed using conventional clinical criteria.¹⁵ Serum glucose, triglycerides, total cholesterol, insulin, and ferritin were measured in the non-fasting state. Renal function was assessed by calculation of creatinine clearance (CrCl) using the Cockcroft–Gault formula, and the appropriate stage of chronic kidney disease (CKD) recorded.¹⁶

Assessment of symptoms and health-related quality of life

Information regarding symptoms, functioning, and quality of life was collected using EORTC QLQ-C30 questionnaires, which include dyspnoea scores.¹⁷

Statistical analysis

Descriptive statistics and non-parametric tests of significance (Spearman's rank correlation coefficient

and Mann–Whitney ‘*U*’ test) were used. PASW version 18 computer software was utilized for data analysis. An *r* value of ≥ 0.4 was taken as a cut-off for strength of correlation and $P < 0.05$ taken to demonstrate significance.¹⁸

Results

Demographics and medical history

Thirty-two patients fulfilling the eligibility criteria were recruited (17 males and 15 females) from a tertiary referral centre. Ten further patients were approached, but either declined to participate or were deemed ineligible. For each variable recorded data were available for at least 30 patients.

Median age at time of assessment was 60 years (range 41–71) with median age at diagnosis 55 years (range 36–69). Patients commenced treatment for symptomatic myeloma in the years 1998–2008. The median time from diagnosis was 6 years (range 2–12)

Table 1 Demographics and treatment history of the cohort (total 32 patients)

Patient demographics	
Age at assessment	Median 60 (range 41–71)
Age at diagnosis	Median 55 (range 36–69)
Duration from diagnosis	Median 6 years (range 2–12)
Sex	17 males, 15 females
Anti-myeloma treatment history	
Lines of treatment received (initial induction + HSCT* counted as a single line)	Median 3 (range 2–6)
HSCT	29 (91%) at least one autologous HSCT 4 (13%) allogeneic HSCT 10 (31%) two HSCT procedures 2 (6%) donor lymphocyte infusion following allogeneic HSCT
Other anti-myeloma chemotherapy	
	32 (100%) cyclophosphamide 32 (100%) melphalan 32 (100%) high-dose steroids 30 (94%) doxorubicin 27 (84%) vincristine 22 (69%) bortezomib (intravenous) 19 (59%) thalidomide 4 (13%) lenalidomide 3 (9%) fludarabine 4 (13%) etoposide 2 (6%) cytarabine 2 (6%) cisplatin 4 (13%) interferon alpha
Radiation therapy	
	13 (41%) any radiotherapy 12 (38%) localized radiotherapy only 1 (3%) total body irradiation and localized radiotherapy 6 (19%) radiotherapy involving thorax

Demographics and anti-myeloma treatment histories of all 32 patients included in the study. Previous anti-myeloma therapy including haematopoietic stem cell transplant procedures, chemotherapy, and radiation therapy is summarized.

*HSCT, haematopoietic stem cell transplantation.

with median time of 5 years (range 1–11) since initial HSCT. Patients had received a median of three (range 2–6) lines of treatment. All patients had undergone at least one HSCT procedure: 29 (91%) at least one autologous HSCT with high-dose melphalan conditioning; 4 (13%) allogeneic HSCT; 10 (31%) two HSCT procedures. Previous chemotherapy and radiotherapy treatments are summarized below (Table 1), and include the use of anthracycline chemotherapy in 30 (94%) patients in the form of doxorubicin, although with a relatively low cumulative dose (<360 mg/m²). Two patients (6%) had received donor lymphocyte infusions after allogeneic HSCT.

Thirteen patients (41%) were obese (BMI >30 kg/m²); 7 (22%) were overweight (BMI 25–29.9 kg/m²); 11 (34%) had a normal BMI (18.5–24.9 kg/m²), and 1 patient (3%) was underweight (BMI <18.5 kg/m²). CrCl was calculated for all patients. Of these, 13 (41%) patients had normal CrCl (≥ 90 ml/min, stage 1 CKD); 14 (44%) patients were in stage 2 CKD (CrCl 60–89 ml/min); 3 (9%) patients in stage 3 CKD (CrCl 30–59 ml/min); and 2 (6%) had severe or end-stage (stage 4–5) CKD (CrCl <30 ml/min).

Cardiovascular assessments

No patient had a history of cardiovascular adverse events prior to diagnosis of myeloma; one patient suffered from two episodes of polymorphic ventricular tachycardia during and after active myeloma treatment, both while being treated for intercurrent sepsis. Heart sounds were normal on standardized clinical examination in all 32 patients. Twenty-four (75%) patients had no pitting oedema; seven (22%) had below-knee oedema, and one (3%) had oedema extending above the knee.

ECGs were analysed for 31 patients. Of these, 17 (55%) patients had ECGs within normal limits and 14 (45%) patients had at least one electrocardiographic abnormality: three patients had limb lead criteria for left ventricular hypertrophy (LVH) and five patients had ECG repolarization abnormalities consistent with LVH. Three patients had ECG evidence of left atrial hypertrophy and three had a prolonged PR interval whilst single patients had atrial fibrillation, isolated left axis deviation, and complete right bundle branch block.

Echocardiography assessments were available for 30 patients; 15 (50%) had normal echocardiograms and for 15 (50%) abnormalities were found. Thirteen patients had left atrial enlargement; six patients had echocardiographic LVH; four had dilatation of the proximal ascending aorta (including one patient with an incidental congenital aortopathy with bicuspid aortic valve); two patients had a dilated left ventricular chamber in diastole; and one had pulmonary hypertension. One patient had mild left ventricular systolic

dysfunction but with a normal NT-pro-BNP level at 3 pmol/l (23 pg/ml). In total 19 (61%) of the 31 patients for whom ECG and/or echocardiography were available had an abnormality of one or both.

Serum NT-pro-BNP level was available for all 32 patients and was raised above the threshold of 15 pmol/l (125 pg/ml) in 16 (50%) patients, with a median level 16 pmol/l (133 pg/ml) (range 2–165 pmol/l (18–1400 pg/ml)). Serum ferritin levels (median 517 pmol/l (230 µg/l), range 16–42 668 pmol/l (7–18 989 µg/l)) were raised above our laboratory reference range (upper limit 337 pmol/l (150 µg/l) for women <50 years; 899 pmol/l (400 µg/l) for all other patients) in 10 (31%) patients, over half of these markedly so (six >2000 pmol/l (890 µg/l)) and serum NT-pro-BNP level correlated significantly with serum ferritin ($P = 0.027$, $r = 0.4$). Serum NT-pro-BNP results also correlated positively with age ($P = 0.001$, $r = 0.5$), and negatively with CrCl ($P = 0.010$, $r = -0.5$) as well as measures of quality of life (see below). We did not observe a significant correlation between abnormalities of echocardiography, ECG, or NT-pro-BNP level and cumulative anthracycline dose, total number of lines of treatment, or with various other potentially cardiotoxic agents, such as cyclophosphamide and thoracic radiotherapy. The relation between serum NT-pro-BNP and the presence of ECG and echocardiographic abnormalities was modest: five subjects had serum NT-pro-BNP >15 pmol/l (125 pg/ml) but no abnormality in ECG or echocardiography whilst 10 had an elevated NT pro-BNP level and an abnormality in ECG or echocardiography.

Respiratory assessments

By standardized clinical history, 3 of 32 patients had previous respiratory diagnoses: emphysema (one patient); bronchiectasis, asthma, and pulmonary lobectomy (one patient); and pulmonary embolism (one patient). Thirty patients (94%) had a normal clinical respiratory examination; two patients had abnormal examinations, one of whom had a prior diagnosis of respiratory pathology.

Spirometry was undertaken in 31 patients, of whom 17 (55%) had normal spirometry results and 14 (45%) had abnormal results. Of those patients with abnormal results, five had a restrictive picture; two an obstructive picture; and seven a mixed picture.

The median value for percentage of predicted FEV1 attained was 79% (range 46–117%) and for FVC was 85% (range 43–116%). Median FEV1/FVC ratio was 81 (range 43–100). Maximum respiratory pressures were recorded for 30 patients. MIP was below calculated lower limit of normal in 10 (33%) (median –54 cm H₂O, range –12 to –102 cm H₂O). For MEP, eight (26%) were below calculated lower limit

of normal (median 96 cm H₂O, range 12–138 cm H₂O).

Lifestyle and cardiovascular risk factors

Three patients (<10%) were current smokers, 12 smoked previously, and the remainder never smoked. No patient reported exceeding the most conservative interpretation of current UK National Health Service recommendations of <21 units of alcohol per week for men and <14 units for women.¹⁹

Eight (25%) patients gave a history of physician-diagnosed hypertension; a further three (9%) patients had either systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on the lower of two readings taken during structured clinical examination, sufficient to warrant follow-up by current criteria.²⁰ Of the patients previously diagnosed with hypertension, five were already on anti-hypertensive medication, two were not on any anti-hypertensives, and medication history was unavailable for one. Only one patient (already known to have type II diabetes mellitus) was already on lipid-lowering medication (simvastatin), but, in the non-fasting state, a further 16 (50%) patients had total serum cholesterol levels ≥5 mmol/l (median 5.0 mmol/l, range 2.2–8.9 mmol/l), and 2 (6%) patients had serum triglyceride levels >5 mmol/l (median 1.5 mmol/l, range 0.7–5.4 mmol/l), cut-off levels in the non-fasting state indicating increased risk of future cardiovascular events.²¹ One patient had a prior diagnosis of type II diabetes mellitus, controlled with metformin; no patient had a non-fasting glucose of >11.1 mmol/l, although serum insulin (median 77 pmol/l (11.1 mIU/l), range 10–1811 pmol/l (1.4–260.8 mIU/l)) was ≥235 pmol/l (33.8 mIU/l) in 8 (26%) of the 31 patients in whom it was measured, a non-fasting level independently associated with an almost twofold increased relative risk of future coronary heart disease events.^{22,23}

Relationships between health-related quality of life and cardiovascular and respiratory parameters

There was a negative correlation between overall health-related quality of life as measured by EORTC QLQ-C30 and serum NT-pro-BNP level ($P = 0.012$, $r = -0.4$). The dyspnoea score of EORTC QLQ-C30 varied widely between individuals (median 33, range 0–100) and correlated with BMI ($P = 0.001$, $r = 0.6$).

Discussion

Modern management strategies have progressively improved the prognosis of myeloma to the extent that it may be regarded as a ‘chronic cancer’ in many patients. However, even when disease activity is controlled, and active treatment discontinued,

patients may be significantly compromised by a cumulative burden of problems related to myeloma, its treatment, and advancing age.

We have analysed a cohort of patients, which arguably represent a typical cross-section of advanced but stable myeloma patients in a tertiary referral HSCT centre. We selected patients with advanced and heavily pre-treated myeloma, and all patients had been exposed to at least one HSCT treatment and one further line of therapy for progressive disease. The majority of patients have had one or two autologous HSCT procedures, and a minority have had an allogeneic HSCT, although all patients have had at least one further treatment for relapsed disease. Importantly, in order to exclude the confounding effects of active myeloma and the acute toxicity of treatment, all patients had controlled disease and were in stable plateau phase and off active treatment.

Although cardiovascular and respiratory late effects are recognized following curative treatments for cancer, including HSCT,^{9,24} this study is the first time that these cardiorespiratory aspects have been examined specifically in long-term survivors of myeloma following several lines of intensive treatment. The major findings were a high prevalence of sub-clinical cardiovascular and respiratory abnormalities, which would be otherwise undetected by clinical examination. The impact of such unrecognized cardiovascular and respiratory abnormalities on aspects of quality of life, including dyspnoea and its effect on physical activity, may be significant, and warrants further investigation. Simple lifestyle modifications may also be important. For example, the majority of our cohort was overweight or obese, which significantly correlated with dyspnoea.

Cardiac abnormalities and cardiovascular risk factors

Despite normal or near normal cardiovascular history and physical examination, we found a high prevalence of sub-clinical cardiac abnormalities on specialized testing, with over 60% having an abnormality of ECG or echocardiogram. In addition, serum NT-pro-BNP level, a marker of cardio-renal strain and potential ventricular dysfunction, was raised (>15 pmol/l (125 pg/ml)) in 50% of patients and to >47 pmol/l (400 pg/ml), the threshold for the investigation of frank heart failure, in 22%.²⁵ The association between raised BNP and the future development of symptomatic heart failure in patients undergoing intensive chemotherapy treatment and stem cell transplantation has been demonstrated in a previous observational study, and confirms the increased risk of overt ventricular failure in those of our cohort with significantly raised levels.²⁶

The majority of the ECG and echocardiographic findings appear to relate to markers of left atrial dilatation and LVH, suggesting a pattern of cardiac injury from myeloma treatments that causes a rise in left ventricular compliance. Myocardial fibrosis or changes of the intercellular matrix may play a role here. It seems likely that the elevated serum NT-pro-BNP levels found in half of our cohort are also due to this effect as there was little evidence of left ventricular systolic dysfunction or major heart valve disease whilst renal dysfunction affected a small proportion of our cohort only. In the long term, raised left ventricular compliance may predispose to the development of atrial fibrillation (as was found in one subject at screening), and in turn to cardio-embolic stroke, as well as a poorer exertional capacity and frank heart failure. It is noteworthy that the NT-pro-BNP level correlated significantly with poorer quality of life scores and a reduced exertional capacity due to early heart failure could be the mechanism of that correlation.

We have found frequent ECG and echocardiogram abnormalities and a high prevalence of elevation of natriuretic peptide levels in a cohort of stable but intensively treated myeloma patients. Historical epidemiological studies shed light on the potential significance of these findings. In a cohort of 831 men aged 55–59 years selected from general US populations, abnormalities on a baseline ECG were found in 17.8% and the presence of such abnormalities predicted a doubling of death rates and coronary events during 11 years of follow-up compared to those with a normal ECG.²⁷ In comparison, 40% of our subjects had such prognostically significant ECG changes according to the criteria of this study (ECG P wave enlargement was not included). The rate of echocardiographic abnormalities in the general population was studied in 3272 people of similar age and gender distribution to our cohort in Norway.²⁸ Echocardiogram abnormalities were found in 9% of the general population, a much lower incidence than the 50% rate of echocardiogram abnormalities in our study. Fifteen subjects in our cohort (47%) had ECG or echocardiogram evidence of left atrial hypertrophy, an abnormality that has been clearly linked to a substantially increased risk of stroke and death in the general population.²⁹ Thus it seems likely that the frequent sub-clinical ECG and echocardiogram abnormalities found in our stable and intensively treated myeloma patients will translate into elevated cardiovascular morbidity and mortality with increasing duration of survival.

The most significant finding in our study is the frequency and magnitude of activation of the natriuretic peptide system. Fifty percent had values above the normal value defined by Hildebrandt *et al.*¹² and,

more strikingly, 41% of our cohort exceeded the age- and sex-stratified upper 97.5th percentile value for NT pro-BNP as defined by Galasko *et al.*³⁰ in healthy subjects. Only 4 of the 32 (13%) myeloma patients had a NT pro-BNP level below the median values defined in their study. Elevated natriuretic peptide levels, particularly NT-pro-BNP, have been shown to predict mortality outcomes in chronic heart failure, hypertension, acute coronary syndromes, those at elevated cardiac risk, and normal populations.³¹ In two community cohorts minimally elevated levels of NT pro-BNP predicted all cause and cardiovascular mortality among apparently healthy subjects^{32,33} and this power persists after adjustment for clinical and echocardiographic factors.³⁴ It is now believed that natriuretic peptide system activation may be secondary to inflammation, fibrosis, and hypertrophy at vascular level as well as clinically overt myocardial stretch and ventricular hypertrophy.³¹ Thus, NT pro-BNP is an important marker for preclinical cardiovascular disease. The question of whether NT pro-BNP levels can identify patients who may benefit from early intervention remains under investigation; reduced rates of progression to heart failure were found in one trial of NT pro-BNP-guided cardiovascular intervention in middle-aged subjects at elevated cardiovascular risk,³⁵ a cohort somewhat analogous to the myeloma patients studied here.

The causes for the cardiovascular abnormalities in our study are likely to be multiple and too complex to explain by a study of this size. Specifically it is not possible to identify a responsible therapeutic agent. The cumulative anthracycline dose was relatively low (at <360 mg/m²) and dose did not correlate with the observed cardiac anomalies. However, both cardiotoxic chemotherapy and the late effects of other potentially cardiotoxic agents, such as multiple doses of 'palliative' thoracic radiotherapy, warrant consideration, both on a routine clinical basis, and in further clinical studies. The correlation between serum NT-pro-BNP and serum ferritin levels supports a link between transfusional iron loading and early cardiac dysfunction and raises the question of whether more accurate measurement of cardiac iron levels by cardiac magnetic resonance imaging, and intervention by venesection and/or iron chelation, should be considered in this patient group.

The limited prognosis of myeloma and the long-term horizon for coronary risk factors have meant that cardiovascular lifestyle modification and the treatment of dyslipidaemia, diabetes, and hypertension were previously challenging to justify. However, increased prevalence of cardiovascular risk factors such as hypertension and dyslipidaemia in the post-transplant setting has been recently recognized in

both autologous and allogeneic HSCT recipients.³⁶ While pre-existing risk factors of diabetes, smoking, and alcohol excess do not appear to be especially raised in our sample compared with the adult UK population as a whole, a significant proportion have evidence of raised cholesterol, triglycerides, and/or insulin, all of which may predict increased risk of future cardiovascular morbidity.^{37,38} In addition, a proportion of our cohort had potentially undiagnosed but treatable hypertension and most were overweight or obese.

The detection of cardiovascular abnormalities in over half of the patients in our cohort raises the question of whether systematic screening may be justified. For example, early detection of cardiovascular abnormalities and risk factors may result in more effective intervention in this expanding group of patients. Given the high proportion of patients with raised serum NT-pro-BNP levels, its measurement for the detection of cardiac dysfunction in intensively treated myeloma patients could be considered as a screening tool for cardiac damage. Patients with early cardiac dysfunction may be treated with angiotensin-converting enzyme inhibitors and other anti-heart failure medication.^{4,9,39} Systematic screening and appropriate medical treatment of risk factors such as dyslipidaemia, hypertension, abdominal obesity, diabetes, and iron overload should also be considered. The use of prognosticators, such as the 10-year CVD risk calculator from the National Heart, Lung and Blood Institute (www.nhlbi.nih.gov), could now be used in long-term myeloma survivors.

Respiratory abnormalities

Few patients in our cohort had abnormal standardized respiratory clinical examinations, but almost half had spirometry results indicating airway pathology. The majority had restrictive or mixed pictures rather than obstructive. In addition, 43% of patients had reduced maximum inspiratory and/or expiratory pressures, causes of which have been shown to include neuromuscular weakness, malnutrition, cachexia, and/or pain.⁴⁰ Whilst spirometry results would be expected to deteriorate with age, it should be noted that expected values are age-corrected and the results from many of our myeloma patients are therefore inferior to those of the general population of a similar age. The cause of the sub-clinical respiratory dysfunction is likely to be multi-factorial, with a combination of disease and treatment factors, including chemotherapy, HSCT, thoracic radiotherapy, and recurrent respiratory infections. Steroid myopathy, a cause of respiratory muscle weakness among cancer patients, may have been a factor as cumulative steroid dosage was high.⁴¹ Evidence for cachexia was rare in the

group, although high starting BMI may have masked weight loss, and a paper recently published by our group has shown that a significant number of these patients have abnormal body composition – specifically ‘sarcopenia’.⁶ Smoking at time of assessment was rare, but the impact of previous smoking may have contributed.

These respiratory data are in agreement with published findings in patients with other heavily treated malignancies, but are previously unreported in myeloma.^{7,42} Limitation in respiratory reserve may have a significant impact on both quality of life and survival in myeloma, where infection remains the leading single cause of death.⁴³ Further investigation is warranted to differentiate the contributions of muscular weakness, pain, fatigue, dyspnoea, high BMI, and genuine airway pathology in this picture as well as any modifiable predisposing or iatrogenic factors. In the meantime, simple measures such as weight/BMI reduction and smoking cessation may improve respiratory function.

Conclusions

Long-term survivors of myeloma are now a distinct and increasing population who accumulate the ‘late effects’ not only of HSCT, but also several other lines of treatment. Our study demonstrates a high prevalence of sub-clinical cardiovascular and respiratory compromise, above that expected in an age-matched non-myeloma population and unlikely to be detected by routine monitoring in the myeloma clinic unless specific screening such as echocardiography or measurement of serum NT pro-BNP levels is undertaken. The impact of such sub-clinical cardiovascular and respiratory abnormalities on aspects of quality of life, including dyspnoea and its effect on physical activity, and on survival may be significant and warrants further investigation. The data in this study provide a starting point for the development of specific cardiovascular and respiratory screening guidance within the long-term comprehensive supportive care of myeloma patients, as well as a basis for future research, including interventional studies.²

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Contributors C.S. collated the study data, assisted with data analysis, and wrote the initial draft of the paper. L.O. analysed the cardiology data and contributed to the sections on cardiovascular abnormalities. E.B. carried out statistical analysis and made significant contributions to the final paper. D.G. made significant contributions to the final draft of the paper. Y.E. carried out medical reviews of patients involved in the study and contributed to the final draft of the paper. S.H.A. was primarily responsible for advising on the analysis of respiratory data and contributed significantly to sections of the paper relating to respiratory abnormalities and other late effects. J.A.S. applied for the grant, wrote the study protocol, provided study oversight, and contributed significantly to all areas of the final draft of this paper.

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