ORIGINAL ARTICLE

European Journal of
Haematology WILEY

Productivity losses in patients with newly diagnosed multiple myeloma following stem cell transplantation and the impact of maintenance therapy

Graham Jackson[1] (ID) | Jayne Galinsky[2] | David E. C. Alderson[3] | Vijay K. D'Souza[3] | Vanessa Buchanan[3] | Sujith Dhanasiri[4] | Simon Walker[3]

[1]Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK

[2]Myeloma UK, Edinburgh, UK

[3]Cogentia Healthcare Consulting, Cambridge, UK

[4]Celgene International, Boudry, Switzerland

Correspondence
David E. C. Alderson, Cogentia Healthcare Consulting, Richmond House, 16-20 Regent Street, Cambridge CB2 1DB, UK.
Email: david.alderson@cogentia.co.uk

Abstract

Objective: This study examined productivity losses in European patients with newly diagnosed multiple myeloma (NDMM) undergoing autologous stem cell transplantation (ASCT), to better understand and model the impact of NDMM and lenalidomide maintenance therapy on productivity from a patient and societal perspective.

Methods: A cross-sectional online patient survey was conducted across the UK, Germany, France, Spain and Italy. A partitioned survival model was used to estimate productivity loss and the impact of maintenance therapy, using human capital (HC) and friction cost approaches.

Results: Of the 115 eligible survey respondents, 76.5% were economically active at the time of diagnosis and highlighted return to work as an important factor affecting their quality of life; only 39.1% of respondents were economically active post-ASCT. HC analyses estimated average total productivity losses per ASCT patient at EUR 290,601 over a 20-year period. Modelling the impact of maintenance therapy alone for these patients reduced average productivity losses by just over 10%.

Conclusion: Patients with NDMM aspire to engage in productive lives post-ASCT, but most are unable to do so. Access to treatments extending remission and supporting engagement in a productive life can have a positive impact both for patients and wider society.

KEYWORDS
autologous transplantation, health services accessibility, multiple myeloma, return to work, surveys and questionnaires

1 | INTRODUCTION

Multiple myeloma (MM) is a life-threatening haematological cancer primarily affecting older patients.[1] In Europe, the median age at MM diagnosis is 72 years, although increasing numbers of patients are diagnosed before the age of 65 years, including those still in employment or with childcare/family responsibilities.[2,3] Therapeutic advances have improved remission and long-term survival rates, particularly for younger patients undergoing autologous stem cell transplantation (ASCT).[1,4,5] However, patients achieving full remission

may not regain their health sufficiently to resume their previous lifestyle and the duration of their remission is often limited.[1,4,5] Compared with other haematological cancers, fewer patients with MM return to work following treatment.[6]

High-dose chemotherapy followed by ASCT is the standard of care for transplant-eligible patients aged ≤70 years.[2,7,8] In Europe, the median age at first ASCT increased from 52.8 years in 1991-1995 to 59.0 years in 2006-2010.[9] Following ASCT, lenalidomide maintenance has been shown to increase overall survival (OS), progression-free survival (PFS) and health-related quality of life (HRQoL).[2,7,10-12] Lenalidomide is currently the only treatment licensed in the European Union for use as post-ASCT maintenance therapy in newly diagnosed MM (NDMM).[2,7,10-12]

In this study, the impact of ASCT on productivity, employment and work in patients with MM was assessed. An online survey was held among patients, and key factors influencing productivity losses and decisions regarding return to work were examined. The overall cost of this productivity loss to society was estimated using an economic model, which was also used to estimate the potential benefits of lenalidomide maintenance therapy for individual patients and wider society.[13-15]

2 | METHODS

2.1 | Patient survey

2.1.1 | Patient recruitment

An online cross-sectional patient survey study was conducted in five European Union (EU5) countries (UK, Germany, France, Spain and Italy) from 27 April 2017 to 15 June 2017. In total, 6 patient advocacy groups were engaged to support patient recruitment and survey design: Myeloma Patients Europe; Myeloma UK; Leukämiehilfe RHEIN-MAIN eV; Arbeitsgemeinschaft Multiples Myelom, Plasmozytom (AMM-Online); Associazione Italiana contro le leucemie-linfomi e mieloma (AIL); and AIL Area Pazienti ONLUS.

Patient advocacy groups recruited patients via a link provided in their communication materials including social media, newsletters, email campaigns and websites. No healthcare professionals were involved in recruitment, and no incentives were provided for survey completion.

2.1.2 | Inclusion criteria

Screening questions verified eligibility for inclusion. Eligible patients with NDMM were ≥18 years old, resident in an EU5 country, had undergone ASCT and were in a state of remission or had relapsed within the previous 3 months.

2.1.3 | Design

The online survey, designed and implemented in accordance with British Healthcare Business Intelligence Association market research and data protection guidelines, was reviewed by an independent project steering committee and participating patient advocacy groups.[16] The survey was developed and tested together with patients from Myeloma UK.

A survey website was created and hosted in the relevant language for each country. Survey objectives, inclusion criteria, approach, data security and terms and conditions were explained on the survey homepage. Participants were required to register with the website to complete the survey. Data were anonymised for analysis.

The survey captured work history and productivity information at two time points: diagnosis and post-ASCT. To minimise responder fatigue, the survey was designed to be completed in approximately 20 minutes and was provided in the relevant local language. A three-step translation and quality assurance process ensured appropriate standards for the website and survey were met in each country. Results were translated into English for analysis.

2.1.4 | Endpoints

Patient demographic information was recorded. A validated work productivity and activity impairment (WPAI) instrument was used to measure disease-related productivity impairment.[17] Participants confirmed their work status at diagnosis and post-ASCT and in the preceding 4 weeks before these time points, together with dates and narratives. Returning to work and factors that influenced this decision were assessed using qualitative questions. Free-text options collected narratives concerning experiences and key events related to work, motivations and plans.

Productivity loss between diagnosis and post-ASCT was estimated for each respondent. The number of lost working hours was estimated by totalling all contracted hours worked over a 4-week period up to diagnosis and comparing it with hours worked over a similar 4-week period post-ASCT. Patients who were unemployed, homemakers or on sick leave were categorised as economically inactive. Those in full-time/part-time employment or self-employed were categorised as economically active.

2.2 | Modelling of productivity losses

2.2.1 | Model structure

A partitioned survival model was created comprising ASCT, remission, progression and deceased health states (Figure 1). The model employed a 20-year time horizon.

Patients entered the model in the ASCT state, which included induction, consolidation and stem cell mobilisation and transplantation phases up to the first day of definitive remission, when maintenance therapy was initiated or observation (no maintenance therapy) was recorded. As this treatment was highly intensive, these phases were combined under one ASCT health state. Patients remained in the ASCT state unless they died. The ASCT health state was assumed to occupy the 1-year period (12 monthly cycles) between diagnosis and the start of maintenance or observation. Data from the European Society for Blood and Bone Marrow Transplantation (EBMT) Registry on patients with MM who underwent a single ASCT between 1999
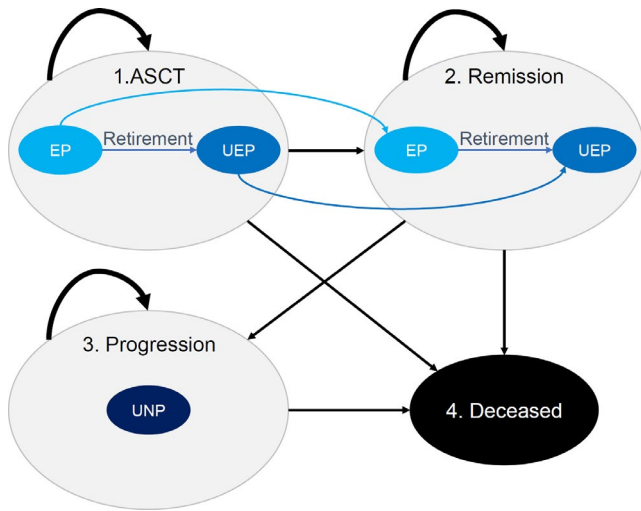
FIGURE 1 Partitioned survival model structure showing each disease state: (1) ASCT, (2) remission (post-ASCT), (3) progression and (4) death. ASCT, autologous stem cell transplantation; EP, employed productive; UEP, unemployed productive; UNP, unemployed not productive [Colour figure can be viewed at wileyonlinelibrary.com]

and 2005 were used to support this 1-year timescale.[18] The percentage of patients transitioning from the ASCT health state to remission or progression at the end of the 1-year period was estimated from Kaplan-Meier survival curves of patients with MM within the EBMT Patient Registry.[18]

Within the ASCT health state, patients are considered unproductive. In the remission health state, patients could be 'employed productive' (EP) or transition to retired or 'unemployed productive' (UEP), based on the probability of retirement in their age group. However, patients (EP and UEP) could lose a high number of productive days due to the burden of NDMM and its treatment. All patients with progressive disease were assumed to immediately become 'unemployed not productive' (UNP). A proportion of EP patients retire immediately upon entering the ASCT health state and become UEP as net contributors to societal productivity. This productive value was based on Eurostat values of unpaid work contributions.[19]

Based on clinical evidence, the model assumed the rate of disease progression could be altered by patients receiving a maintenance therapy.[2,7,10-12] Productivity losses for the population cohort were estimated for patients with NDMM not receiving maintenance therapy and compared with those receiving lenalidomide. Lenalidomide maintenance therapy was used to inform the survival curve modelling, as it is the only maintenance therapy licensed in the EU5 countries.[2,7,10-12] Losses were estimated on both a per-patient basis over the 20-year time horizon and as the total aggregated losses from a 1-year incident patient cohort.

2.2.2 | Patient cohort

The patient cohort comprised patients with NDMM eligible for and undergoing ASCT from the EU5 countries. The model assumed a

median patient age of 57 years, which was based on the mean age of respondents to the survey. All patients were assumed to have received ASCT and patients under 65 years were assumed transplant-eligible. Cohort size was based on incidence rates by age band for each country and was adjusted to reflect the number of patients undergoing ASCT, aligning with the rate observed in participating countries in 2014 per the EBMT activity survey report.[20]

2.2.3 | Survival modelling

To model the journey of patients who received either lenalidomide maintenance therapy or observation in remission from the end of the 1-year period, parametric OS and PFS curves were fitted to pooled patient-level data from three randomised clinical trials (RCTs) examining post-ASCT lenalidomide maintenance therapy: Cancer and Leukemia Group B (CALGB) 100 104,[21] Intergroupe Francophone du Myélome (IFM) 2005-02[22] and Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA).[23] RCT data were used in preference to EBMT data, as the EBMT Patient Registry data included use of maintenance therapies not licensed in the EU5 countries (eg thalidomide) and did not stratify outcomes by receipt of maintenance.

Curves were fitted using a combination of statistical goodness-of-fit criteria and visual assessment of fit. Proportional hazards between the maintenance therapy and on-trial arms were assumed. The number of patients in the progression health state was calculated as the difference between the OS and remission survival curves.

2.2.4 | Productive days lost in each health state

Two data sources were used to estimate productive days lost per health state: our patient survey from 2017 and a study on the cost of illness in patients with MM in Italy (CoMiM) from 2008.[24] The CoMiM study collected days lost for employed and unemployed patients by treatment phase.[24] Our patient survey provided similar data for patients with NDMM in remission post-ASCT in the EU5 countries during 2017.

2.2.5 | Human capital (HC) approach

Productivity was estimated for three cohorts: the general population, patients with NDMM receiving ASCT plus maintenance therapy and patients with NDMM receiving ASCT and observation only. Earnings or productive output (EP or UEP) of the three cohorts over the 20-year time horizon were projected by applying estimates of absenteeism for NDMM patients to Eurostat employment data for the general population.[18] Short-term absenteeism following ASCT (<3 weeks/month or return to work within 1 year) incurred a productivity loss equivalent to the gross wages (pro rata) of the worker. Long-term absenteeism following ASCT (leaving the workforce) incurred a productivity loss equivalent to the gross wages of the worker to the end of the model time horizon. All costs were discounted, taking the year of diagnosis as the base year.

TABLE 1 Rules applied to the friction period for patients in employment

Situation/circumstance	Rule applied
Temporary sickness: periods shorter than or equal to the friction period	Productivity loss was the time absent from work × age-adjusted and gender-adjusted gross earnings for that period × 80% (elasticity of annual working time vs labour productivity)
Long-term absence/disability: periods longer than the friction period	Productivity loss was the friction period × age-adjusted and gender-adjusted gross earnings for that period × 80% (elasticity of annual working time vs labour productivity). Where available, the cost of recruitment and training was added to the friction cost estimate
Mortality during long-term absence/disability: periods longer than the friction period	No lost productivity was assumed because these workers had been accounted for at the point of long-term absence
Mortality while employed	Productivity loss was estimated as the friction period × age-adjusted and gender-adjusted gross earnings for that period × 80% (elasticity of annual working time vs labour productivity)

2.2.6 | Friction cost (FC) approach

The FC approach compared the same three cohorts as the HC approach, assuming productivity loss was incurred until replacement labour was found (ie the friction period). The proportion of productivity loss during the friction period was assumed to be 80% of the gross wage during the friction period (elasticity of annual working time vs labour productivity).[14]

The friction periods in different countries were informed by data from Erdogan-Ciftci and Koopmanschap (2011).[15] Table 1 depicts the cost limitation rules that were applied for the friction period for employed patients. The cost of recruitment and training was added to the FC estimate. Table 2 summarises the model inputs.[13,15,18,20-25]

3 | RESULTS

3.1 | Patient survey

3.1.1 | Patient demographics

Of the 115 respondents included in the study, 62 (53.9%) were female and 92 (80.0%) were still in remission post-ASCT (Table 3). Most patients were based in the UK (n = 63; 54.8%) or in Germany (n = 29; 25.2%). Patients' mean age at diagnosis was 57 years, with 79.0% aged ≤ 60 years at diagnosis (n = 91). Post-ASCT, the number of patients aged ≤60 years shifted to 55.7% (n = 64).

3.1.2 | Survey completion

The mean time between diagnosis and survey completion (post-ASCT) was approximately five years. However, the mean time since diagnosis decreased with increasing age, from 73 months in patients aged <50 years to 60 months in patients aged 50-65 years and 39 months in patients aged >65 years. The time between ASCT and

survey completion post-ASCT showed a similar pattern (55 vs 45 vs 29 months, respectively) (data not shown).

3.2 | Quantitative endpoints

3.2.1 | Economic activity and employment status

Post-ASCT, 39.1% of patients (n = 45) were EP, vs 76.5% (n = 88) at the time of diagnosis. Overall, 45.2% of respondents (n = 52) did not change employment status between diagnosis and survey completion. Of the remaining respondents (n = 63, 54.8%), most changed from full-time employment to retirement (20% of patients retired at diagnosis vs 45% of patients at survey completion) (Figure 2). Self-employed respondents were least likely to change their employment status.

The largest change in employment status was observed in patients aged 50-65 years; 87% of those in full-time employment at the time of diagnosis switched to retirement, part-time employment or sick leave at survey completion. For patients choosing to retire at age 50-65 years, 80% stated in the survey that this choice was due to their diagnosis rather than their approaching retirement age or previous planning; only 11% had originally planned to retire around this age.

Of EP patients aged <65 years at diagnosis, 54% expressed an intent to return to work post-ASCT (61% of patients aged <50 years vs 48% of patients aged 50-65 years). The actual return to work rate was 63% for those aged <65 years; 52% were still employed post-ASCT. Overall, 79% of patients with NDMM who expressed an intention to return to work at the time of diagnosis did so at survey completion.

3.2.2 | Working hours lost

Data from survey respondents showed worked hours dropped by 59.8% between diagnosis and survey completion (13 168 vs 5296 hours, respectively). In total, 79.8% of this loss was a result of

TABLE 2 Summary of inputs for human capital and friction cost productivity models

Parameter	Value	Assumptions	Source
Epidemiology			
Age and sex-adjusted incidence of MM by country	Multiple values	N/A	GLOBOCAN, Cancer Research UK[25]
Total population by age and sex by country	Multiple values	N/A	Eurostat table [demo_pjangroup][18]
Employment			
Percentage of population employed by age and sex by country	Multiple values	N/A	Eurostat table [lfsi_emp_a][18]
Annual gross wage of employed workers by age and sex by country	Multiple values	N/A	Eurostat table [earn_ses14_28][18]
Annual gross wage of unemployed productive workers by age and sex by country	Multiple values	Gross wage of 'elementary' occupations	Eurostat table [earn_ses14_28][18]
Adjusted factor for gross wage of unemployed productive workers, %	81.0	Contributing family workers work fewer h per wk than employed workers	Eurostat table [lfsa_ewhuis][18]
Probability of retirement by age and sex by country	Multiple values	Assumed to be the same for standard and MM populations	Eurostat table [lfso_06finiagps][18]
MM patient productivity			
Percentage of patients retiring at diagnosis of MM, %	31.0	Patients retire at model entry	Patient survey
Unproductive d/mo in ASCT health state, d	10.6		Petrucci et al, 2013[24]
Unproductive d/mo in remission health state, d	4.0	Not influenced by receipt of maintenance therapy	Petrucci et al, 2013[24]
Friction cost parameters			
Elasticity of annual working time vs labour productivity	0.8	Dutch estimate as no international values were identified	Koopmanschap & Rutzen, 1996[13]
Friction period, UK, d	80.0	N/A	Erdogan-Ciftci & Koopmanschap, 2011[15]
Friction period, France, d	60.0	N/A	Erdogan-Ciftci & Koopmanschap, 2011[15]
Friction period, Germany, d	92.0	N/A	Erdogan-Ciftci & Koopmanschap, 2011[15]
Survival parameters			
Duration of ASCT health state, mo	12.0	N/A	Cook et al, 2011[20]
Patients who survive ASCT before receiving maintenance, %	95.0	Exponential distribution assumed for cycle probability of survival in ASCT	Cook et al, 2011[20]
Patients who enter remission health state following diagnosis and ASCT, %	0.84	N/A	Cook et al, 2011[20]
Parametric survival curve informing OS	Weibull	Best fit curve as defined by AIC and BIC criteria and visual assessment	Transplant-eligible patient data[21-23]
Parametric survival curve informing PFS	log logistic	Best fit curve as defined by AIC and BIC criteria and visual assessment	Transplant-eligible patient data[21-23]

Abbreviations: AIC, Akaike information criterion; ASCT, autologous stem cell transplantation; BIC, Bayesian information criterion; GLOBOCAN, Global Cancer Incidence, Mortality and Prevalence; MM, multiple myeloma; OS, overall survival; PFS, progression-free survival.

respondents not returning to work following ASCT; 16.6% of the loss was due to reduced working hours and the remainder to absenteeism associated with disease impact (Table 4). For those who returned to work, working hours were reduced by 24.7% post-ASCT vs at diagnosis. Respondents aged >50 years reported more productivity losses than did those aged <50 years.

3.2.3 | WPAI

Mean overall work impairment due to MM was 32.7% in patients currently working; absenteeism was 8.2%. Mean absenteeism was 3.7% vs 14.6% in patients aged <50 years or 50-65 years, respectively (Table 4). However, mean overall work impairment was comparable

TABLE 3 Respondent demographics of patients with MM (N = 115)

Variable	Categories	Number of patients, n (%)
Gender	Male	53 (46.1)
	Female	62 (53.9)
Current MM status	In remission	92 (80.0)
	Relapsed	16 (13.9)
	Unsure	7 (6.1)
Mean age of survey respondents at time of diagnosis		57 years
Age group at diagnosis, y	≤40	16 (13.9)
	41-45	12 (10.4)
	46-50	19 (16.5)
	51-55	12 (10.4)
	56-60	32 (27.8)
	61-65	20 (17.4)
	66-70	2 (1.7)
	>70	2 (1.7)
Age group post-ASCT, y	≤40	10 (8.7)
	41-45	7 (6.1)
	46-50	14 (12.2)
	51-55	7 (6.1)
	56-60	26 (22.6)
	61-65	24 (20.8)
	66-70	21 (18.2)
	>70	6 (5.2)
Educational attainment at survey completion	Primary	1 (0.9)
	Secondary/high school	25 (21.7)
	Vocational/technical	9 (7.8)
	Higher degree	75 (65.2)
	Other	3 (2.6)
	Not provided	2 (1.7)
Country of residence	UK	63 (54.8)
	Germany	29 (25.2)
	Spain	15 (13.0)
	France	5 (4.3)
	Italy	3 (2.6)

Abbreviations: ASCT, autologous stem cell transplantation; MM, multiple myeloma.

across these age groups (31.8% vs 34.1% in patients aged <50 years and 50-65 years, respectively).

3.3 | Qualitative data

Key factors driving the decision to return to work included financial pressures and the desire to lead a 'normal' productive life (cited by 22% and 41% of respondents who returned to work, respectively).

Of those not returning to work, 41% felt they lacked the strength or fitness required to perform their job, 18% were unable to work due to their disease or treatment, and 18% highlighted changing priorities as a reason to not return to work. At diagnosis, 9% of patients reported not wanting to return to work, while 55% rated the personal goal of returning to work as important.

3.4 | Modelling of productivity losses

3.4.1 | HC approach

Using the HC approach, the productivity loss was estimated for the cohort of patients with NDMM undergoing ASCT vs an age- and sex-matched general population cohort. The model outcomes estimate the value of losses triggered in 2017 using the transplant-eligible patients diagnosed with MM during that year, with losses totalled and discounted over a 20-year time horizon (which, for most patients, would capture their peak productive years).

Across the EU5 countries, the total average per-patient productivity losses ranged from EUR 240 000 in Spain to EUR 308 000 in Germany. Lenalidomide maintenance therapy reduced the average productivity loss by EUR 29 126; the average productivity loss was EUR 290 601 for patients receiving observation only, compared with EUR 261 000 per patient using lenalidomide maintenance therapy. For example, from an individual patient perspective, the total productivity loss post-ASCT for a 40-year-old patient in the UK who did not receive maintenance therapy was estimated at EUR 500 000 using the HC approach. With the use of maintenance therapy, this productivity loss was estimated to be reduced by EUR 43 000 to a value of EUR 457 000.

3.4.2 | FC approach

Based on the FC approach, productivity losses per patient were estimated at EUR 2575 during the friction period. The modelled impact of maintenance treatment reduced this value by approximately EUR 77.

4 | DISCUSSION

This study examined productivity losses in patients with NDMM post-ASCT to understand the impact of NDMM and its treatment on productivity, as well as the potential benefits of maintenance therapy from a patient and societal perspective. Patient survey data showed that the disease and treatment burden of NDMM were associated with productivity losses on a personal level post-ASCT, and highlighted that losses were largely due to patients retiring or not returning to full-time work. The economic model estimated considerable productivity losses following a diagnosis with MM and subsequent ASCT; however, data indicating maintenance therapy may improve patient HRQoL suggests social benefits beyond the economic benefits revealed in the model.[26]

FIGURE 2 Employment status at the time of diagnosis and survey completion [Colour figure can be viewed at wileyonlinelibrary.com]
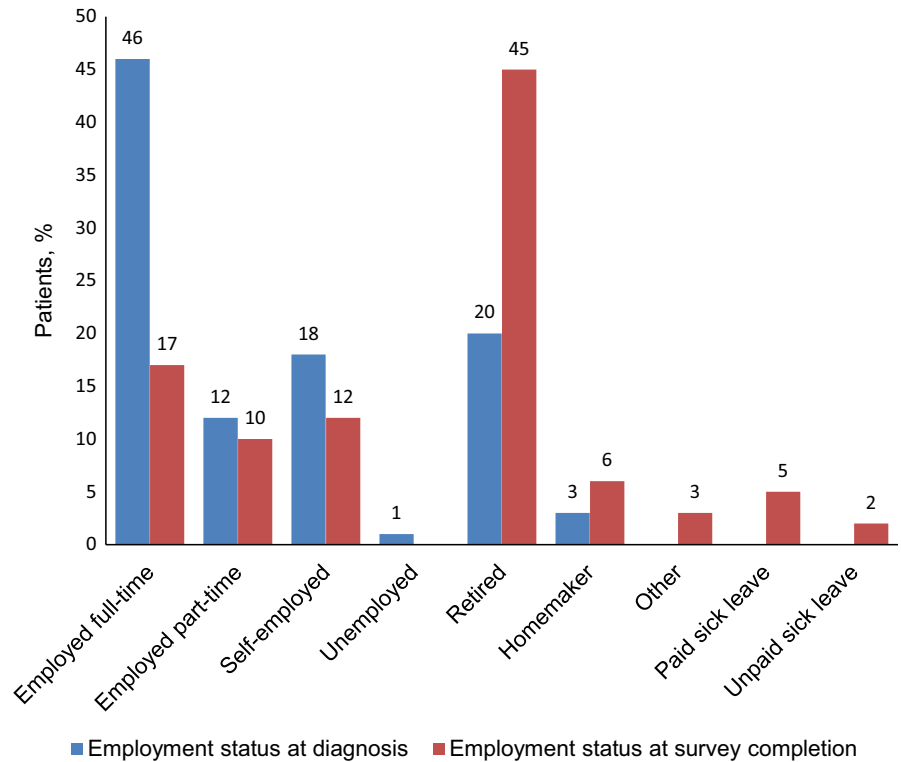
The survey revealed that although most patients (76.5%) were economically active at diagnosis, this figure fell to 39.1% post-ASCT. Overall, a 60% reduction in working hours was demonstrated, and the proportion of patients in full-time employment decreased from 46% at diagnosis to 17% post-ASCT. Productivity loss was greater in patients aged 50-65 years vs those <50 years: 87% switched from full-time employment to retirement, part-time employment or sick leave. Overall WPAI instrument results were similar across the age groups. Absenteeism was higher in patients aged >50 years, which may have contributed to productivity losses in this group, in addition to the decision to retire. These results emphasise the direct impact of NDMM on patients living with the disease, and on their families.

Many survey respondents expressed an intention to return to work following diagnosis. The desire to lead an active life post-ASCT was prioritised ahead of financial considerations for those intending to return to work. However, 80% of overall productivity loss was due to patients feeling unable to return to work post-ASCT, with many stating that they lacked the fitness to conduct daily duties effectively. These findings support a recent international systematic review of productivity loss across a broad range of cancers, including leukaemia, which highlighted that productivity losses were often associated with disease progression and patients feeling unable to carry out their previous roles.[27]

Whereas the survey provided individual perspectives on the productivity loss and impact of ASCT on work-life attitudes, the model used a general approximation for the proportion of the incident population who were transplant-eligible and received ASCT. If the proportion of patients receiving ASCT increased in the future, the model would underestimate the productivity losses. The model cohort was based on the average age of survey respondents (57 years)

and was adjusted to correspond to the real-world ASCT experience. In the model cohort, 28% of patients were <50 years old with several potentially productive years of employment ahead until reaching the national retirement age of their country (range: 62-66 years for the countries examined).[25] Although patients aged >50 years included in the cohort may have had fewer productive years ahead of them, these patients were more likely to be at the peak of their earning potential and would have incurred considerable losses as a result of their employment status changing.

HC analysis estimated productivity loss for this cohort of patients at an average of EUR 290 601 per patient over the 20-year time horizon. The model assumed that maintenance therapy would extend the period during which patients would remain EP or UEP, based on evidence from clinical trials demonstrating improvements concerning remission and HRQoL post-ASCT.[10-12,20-22] Although other therapies such as ixazomib have been studied as maintenance therapy in this population,[28] data from lenalidomide studies were used for estimating the impact of maintenance therapy on productivity as lenalidomide is the currently approved standard maintenance therapy in this setting.[2] HC analysis estimated that lenalidomide maintenance therapy could reduce productivity losses by EUR 29 126 per patient across the EU5 countries. This reduction in productivity losses reflected the estimated increase in time spent in remission and a reduction in the time spent in the progression health state, as well as a decrease in the proportion of patients who die. However, the reduction in productivity loss could be underestimated, as returning to work is multifactorial and could continue beyond patients' first relapse. Compared with therapies that require intravenous and subcutaneous administration, the use of oral maintenance therapies,

TABLE 4 Loss of working hours and mean work impairment in patients according to the WPAI instrument in post-ASCT NDMM population by age group

	Age group			
	All	<50 y	50-65 y	>65 y
Work completed at diagnosis, h	13 168	6368	6576	224
Type of work loss, h				
Not returning to work	6280	2200	3896	184
Reduction in working hours	1312	456	856	0
Due to MM during work	280	102	178	0
Work completed post-ASCT, h	5296	3610	1646	40
Total losses, h	7872	2758	4930	184
Type of work impairment due to MM, mean %				
Work time missed (absenteeism)	8.2	3.7	14.6	N/A
Impairment while working (presenteeism)	28.9	28.5	29.3	N/A
Overall work impairment	32.7	31.8	34.1	N/A
Activity impairment	32.6	28.2	38.2	N/A

Abbreviations: ASCT, autologous stem cell transplantation; N/A, not available; NDMM, newly diagnosed multiple myeloma; WPAI, work productivity and activity impairment.

such as lenalidomide, could also help drive down both administration-related and indirect costs (eg by reducing the number of journeys a patient is required to make).[29]

Previously, Petrucci et al[24] used the HC approach to examine work-related productivity in patients with MM post-ASCT and estimated annual losses of between EUR 9538.30 and EUR 17 612.40 per patient, which are lower than the productivity losses found in our study. However, the Petrucci et al study included many retired patients (mean age 66.4 years), and losses were reported on an annual basis and excluded unpaid work. In contrast, the patient cohort examined in our study was assumed to be of working age (<65 years), and as a result, the productivity losses would be expected to be much greater.

The two modelling approaches generated different values for productivity loss.[13] The HC method estimates the value of potentially lost production by assuming that workers are not replaced when they take short- or long-term leave. Therefore, lost productivity is a function of what that worker would have earned had they not been absent. In contrast, the FC approach focusses on the cost of change and transition and assumes the loss of the individual from the workforce was compensated for relatively quickly by a successor.[13-15] Both approaches have their own merits: the HC approach tends to be used more frequently and considers productivity losses from the perspective of the individual, whereas the FC approach considers them from the perspective of the employer. This is summarised in Table S1. Our model demonstrates

the value of maintenance therapy in reducing productivity losses by extending the period during which patients with NDMM can maintain their employment post-ASCT.

Because our survey was performed online, and respondents were recruited through patient advocacy groups, the study may have attracted patients that were more proactive, motivated or in a better state of general health than the wider post-ASCT NDMM population. The survey relied on self-reported patient information, meaning responses regarding clinical outcomes might not be as robust as clinical records. However, responses were consistent within each age bracket, indicating that the data were reflective of the current circumstances of most patients with post-ASCT NDMM in each age category examined. Also, since most survey respondents were based in the UK and Germany, the results may reflect the situation in these countries more closely than that in the other countries surveyed (ie France, Italy and Spain).

One limitation of the economic model was the assumption that patients who progressed become unproductive, whereas patients may receive second-line treatments and enter another period of extended remission, during which they may work. This scenario would reduce the productivity losses estimated by the model, particularly using the HC approach. In addition, it is important to note that work choices made by patients could be affected by their receipt of maintenance therapy, increasing the potential for further savings.

This study demonstrates the significant impact of NDMM on productivity from an individual and societal perspective as well as the importance of supporting patients with NDMM post-ASCT to return to employment.

The survey data demonstrate that productivity losses incurred by patients with NDMM aged <65 years are driven by decisions to retire or leave employment due to disease and treatment burden. This represents a change from patient aspirations at diagnosis, when most patients with MM intend to return to employment post-ASCT and continue leading productive lives.
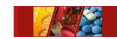
The significant productivity losses experienced by patients with NDMM post-ASCT aged <65 years are reduced by lenalidomide maintenance therapy, according to the model and HC approach.

Provision of support or treatments enabling patients to fulfil their work and productivity aspirations provide additional benefits relating to HRQoL and well-being, in addition to financial motivations.

ACKNOWLEDGEMENTS

Corporation. The authors had full access to the data and are fully responsible for content and editorial decisions for this manuscript.

CONFLICT OF INTEREST

Dr Jackson reports consultancy for Amgen, Celgene Corporation, Chugai, Johnson & Johnson, and honoraria from Takeda. Dr Galinsky has nothing to disclose. Mr Alderson has nothing to disclose. Dr D'Souza has nothing to disclose. Dr Buchanan has nothing to disclose. Dr Walker reports employment at Cogentia Healthcare Consulting Ltd. Dr Dhanasiri reports employment at and equity ownership in Celgene Corporation.

ORCID

Graham Jackson https://orcid.org/0000-0003-0756-969X

REFERENCES

1. Gozzetti A, Candi V, Papini G, Bocchia M. Therapeutic advancements in multiple myeloma. *Front Oncol*. 2014;4:241.
2. Moreau P, San Miguel J, Sonneveld P, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28:iv52-iv61.
3. Cancer Research UK. Myeloma incidence statistics. 2013–2015. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/incidence#heading-Two. Accessed February 4, 2018.
4. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood*. 2008;111:2516-2520.
5. Brenner H, Gondos A, Pulte D. Recent major improvement in long-term survival of younger patients with multiple myeloma. *Blood*. 2008;111:2521-2526.
6. Horsboel TA, Nielsen CV, Nielsen B, Jensen C, Andersen NT, de Thurah A. Type of hematological malignancy is crucial for the return to work prognosis: a register-based cohort study. *J Cancer Surviv*. 2013;7:614-623.
7. Gay F, Engelhardt M, Terpos E, et al. From transplant to novel cellular therapies in multiple myeloma: European myeloma network guidelines and future perspectives. *Haematologica*. 2018;103:197-211.
8. National Institute for Health and Care Excellence. Myeloma: diagnosis and management. February 2016. https://www.nice.org.uk/guidance/ng35/resources/myeloma-diagnosis-and-management-pdf-1837394042821. Accessed February 4, 2018.
9. Auner HW, Szydlo R, Hoek J, et al. Trends in autologous hematopoietic cell transplantation for multiple myeloma in Europe: increased use and improved outcomes in elderly patients in recent years. *Bone Marrow Transplant*. 2015;50:209-215.
10. Moreau P, Attal M, Facon T. Frontline therapy of multiple myeloma. *Blood*. 2015;125:3076-3084.
11. Lipe B, Vukas R, Mikhael J. The role of maintenance therapy in multiple myeloma. *Blood Cancer J*. 2016;6:e485.
12. Sengsayadeth S, Malard F, Savani BN, Garderet L, Mohty M. Posttransplant maintenance therapy in multiple myeloma: the changing landscape. *Blood Cancer J*. 2017;7:e545.
13. Koopmanschap MA, Rutten FF. A practical guide for calculating indirect costs of disease. *Pharmacoeconomics*. 1996;10:460-466.
14. Kigozi J, Jowett S, Lewis M, Barton P, Coast J. Estimating productivity costs using the friction cost approach in practice: a systematic review. *Eur J Health Econ*. 2016;17:31-44.
15. Erdogan-Ciftci E, Koopmanschap MA. Estimation of productivity costs using the friction cost method: new evidence using national data. *Value in Health*. 2011;14:A235-A236.
16. BHBIA. Legal and ethical guidelines for healthcare market research. 2017. https://www.bhbia.org.uk/guidelines/legalandethicalguidelines.aspx. Accessed February 4, 2018.
17. Reilly MC, Zbrozek AS, Dukes E. The validity and reproducibility of a work productivity and activity impairment measure. *Pharmacoeconomics*. 1993;4:353-365.
18. Cook G, Jackson GH, Morgan GJ, et al. The outcome of high-dose chemotherapy and auto-SCT in patients with multiple myeloma: a UK/Ireland and European benchmarking comparative analysis. *Bone Marrow Transplant*. 2011;46:1210-1218.
19. European Commission. Eurostat data. http://ec.europa.eu/eurostat/web/lfs/data/database. Accessed February 4, 2018.
20. Passweg JR, Baldomero H, Bader P, et al. Hematopoietic stem cell transplantation in Europe 2014: more than 40 000 transplants annually. *Bone Marrow Transplant*. 2016;51:786-792.
21. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012;366:1770-1781.
22. Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012;366:1782-1791.
23. Palumbo A, Cavallo F, Gay F, et al. Autologous transplantation and maintenance therapy in multiple myeloma. *N Engl J Med*. 2014;371:895-905.
24. Petrucci MT, Calabrese E, Levi A, et al. Cost of illness in patients with multiple myeloma in Italy: the CoMiM study. *Tumori*. 2013;99:193-202.
25. Cancer Research UK. GLOBOCAN data. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/incidence. Accessed February 4, 2018.
26. Nielsen LK, Jarden M, Andersen CL, Frederiksen H, Abildgaard N. A systematic review of health-related quality of life in longitudinal studies of myeloma patients. *Eur J Haematol*. 2017;99:3-17.
27. Kamal KM, Covvey JR, Dashputre A, et al. A systematic review of the effect of cancer treatment on work productivity of patients and caregivers. *J Manag Care Spec Pharm*. 2017;23:136-162.
28. Dimopoulos MA, Gay F, Schjesvold F, et al. Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial. *Lancet*. 2019;393:253-264.
29. Mankinen P, Vihervaara V, Torvinen S, Martikainen J, Soini E. Costs of administration, travelling, and productivity losses associated with hospital administration of multiple myeloma drugs in Finland. *J Med Econ*. 2019;22:328-335.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.