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Factors Influencing the Outcome of a Second Autologous Stem Cell Transplant (ASCT) in Relapsed Multiple Myeloma: A Study from the British Society of Blood and Marrow Transplantation Registry

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Autologous stem cell transplant as primary (first ASCT) therapy in multiple myeloma (MM) is standard practice. The role of a second ASCT as management of relapsed disease remains uncertain. We conducted a retrospective case-matched control analysis on patients (n = 106) who underwent a second ASCT compared with conventional chemotherapy (CCT) as for relapsed MM. The median age was 53 years (range: 26-75) and median follow-up 48 months (range: 8, 136). The cumulative incidence of 1 and 5 years nonrelapse mortality (NRM) was 7% (95% confidence interval [CI] 3%-13%) and 12% (95% CI 7%-19%), with a second ASCT inducing a greater partial remission (PR) rate of 63%. The 4-year overall survival (OS) rate was 33% (95% CI 24%-45%). Factors associated with improved OS and progression-free survival (PFS) included younger age (<55 years), β_2MG <2.5 mg/L at diagnosis, a remission duration of >9 months from first ASCT, and a greater PR in response to their first ASCT. In a matched-cohort analysis with patients receiving conventional chemotherapy (CCT), the same factors were associated with improved OS, with the exception of a longer remission duration (>18 months) from first ASCT. Second ASCT in relapsed MM is associated with superior OS and PFS compared with CCT, offering a potential consolidative option for selected patients.

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INTRODUCTION

Multiple myeloma (MM) remains an incurable plasma cell tumor for the majority of patients. Its median age of presentation is 70 years [1]. For younger patients with MM, the standard of care is induction therapy consolidated with high-dose melphalan (HDM) and autologous peripheral blood stem cell (ASCT) rescue [2-4]. Studies to date clearly demonstrated that patients who receive ASCT as part of their initial management will have an increased event-free survival (EFS) and overall survival (OS), compared with those receiving conventional chemotherapy (CCT) [4-6]. Almost all patients with MM will relapse at some stage following initial therapy—the majority within 3 years of an ASCT. However, the prognosis and optimal therapy for patients relapsing after this initial intensive therapeutic approach is less certain. The recent introduction of novel agents such as Thalidomide, Lenalidomide, and Bortezomib has resulted in effective disease responses, and although the durability of such responses remain

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to be tested, their use is associated with an improved survival [7-9]. Nonetheless, many questions about management of relapsed disease remain.

One clinical treatment option in the management of relapsed disease is a second ASCT. The first report of the use of ASCT as salvage therapy demonstrated a significantly prolonged survival compared with standard therapy [10]. Favorable prognostic variables in these patients were an initial remission of >12 months and a low β2m (≤2.5 mg/L) at diagnosis. More recently, a retrospective study of 26 patients who underwent a second ASCT as salvage therapy demonstrated a trend in improved OS and EFS, a though 2 similar single institutional studies were unable to definitively demonstrate the true efficacy of such a strategy [11-13]. To date, there have been no randomized controlled clinical studies performed to examine the role of a second ASCT in relapsed disease, and importantly identifying factors that may delineate which patients may benefit more from a second ASCT. Therefore, we report the results of a case-matched retrospective study examining the role of a second ASCT in the management of relapsed disease following a previous ASCT, identifying factors associated with disease-free (DFS) and OS.

PATIENTS AND METHODS

Eligible patients were identified from the British Society for Blood and Marrow Transplantation (BSBMT) Data Registry and additional patient-specific data was acquired directly from individual centers. Consent for data to be registered on the BSBMT Registry for use in activity, outcome, and research analysis was obtained at the time of transplantation, in line with European Bone Marrow Transplant Registry directives. This study was approved and registered by the BSBMT Clinical Trials Committee. Patients undergoing multiple ASCT as part of a tandem program were excluded. From a cohort of patients who underwent a first ASCT between 1990 and 2002, there were 312 ASCT in 149 patients, of which 11 were third transplants and 1 a fourth, with 1 patient having no available data and therefore 15 were excluded. Thus, the study cohort consisted of 296 first and second transplant pairs performed in 148 patients.

Identification of Controls for Case-Control Analysis

An appropriate control group was identified using the following criteria: gender, age at first transplantation, β_2 microglobulin (β_2MG) at diagnosis, duration of first remission (whether complete or partial), status at first transplantation, year of first transplantation, total body irridiation (TBI)-containing conditioning regimen, time from diagnosis to first transplantation, response to first transplantation, immunoglobulin isotype, and disease stage at diagnosis. Of these factors, age at first transplantation, year of first transplantation, and β_2MG at diagnosis were independently statistically significant by Cox regression for OS. Data for β_2MG at diagnosis were available for only 72 of the 148 patients (49%). Thus, controls were matched on age at first transplantation, status at first transplantation, and length of remission after first transplantation (>9 → 24 months). It was also decided to match for year of transplantation (in 4-year intervals) to account for procedural and supportive care changes.

All first transplantations performed in the same time interval were then identified from the BSBMT Registry. The BSBMT Registry identified 2896 HDM/ASCT performed for MM in this interval, of which 505 were multiple transplantations (either tandem or second transplantations on relapse), leaving 2391 single ASCT. Of these, 1578 had complete data on all the variables required for matching described above. Finally, 525 of these had relapsed after the first transplantation, and in 342 of these we had complete data concerning the relapse, including adequate follow-up after relapse. Thus, the case-matched control cohort was selected from these 342 patients. From the initial study cohort of the 148 patients who had second ASCT, 106 were matched on all the criteria with 106 patients who had single ASCT in the control group, thus completing the study case-matched cohorts for analysis.

Statistical Analysis

The original 2 cohorts of patients were compared using Fisher exact test for categoric data and the Wilcoxon test for continuous data. Overall progression-free survivals (PFSs) were calculated by Kaplan-Meier, and univariate comparisons were made within the second transplant group by the log-rank test for binary or categoric variables and by Cox proportional hazard regression for continuous and ordered categoric variables and for multivariable analyses. These analyses identified the prognostic factors in the cohort. The 2 cohorts (all 148 second transplantations and all 342 single transplantation patients) were compared using stratified Cox regression, stratifying on the prognostic factors identified in the preliminary analysis described above. Matching patients were selected from the single transplantation group to match as many as possible of the second transplantation cohort on all the prognostic factors, giving 2 case-matched cohorts of n = 106 patients each. Comparisons between these 2 groups were made using the Wilcoxon matched-pairs test for categoric variables and the stratified Cox regression for the survival variables.

RESULTS

Patient Characteristics

The patient and disease-specific characteristics are illustrated in Table 1. For patients undergoing

Table 1. Patient Characteristics by Treatment at Relapse

	All Patients		Case-matched Control		*P*	*P*
Year	Second ASCT	CCT	Second ASCT	CCT	All	Case-Matched
n	148	342	106	106		
Median age at diagnosis (years; range)	52 (25, 72)	53 (25, 70)	53 (25, 72)	53 (25, 70)	.037	.843
Median age at first ASCT (years; range)	53 (26, 75)	55 (25, 76)	54 (26, 75)	54 (25, 76)	.019	.413
Sex: female/male (%)	45/103 (30%/70%)	111/219 (34%/66%) *14 u/k*	33/73 (31%/69%)	35/66 (35%/65%) *5 u/k*	.500	.590
Disease subtype:		*51 u/k*		*13 u/k*	.418	.851
IgG	84 (57%)	161 (55%)	60 (57%)	55 (59%)		
IgA	30 (20%)	77 (26%)	23 (22%)	22 (24%)		
Light chain disease	28 (19%)	42 (14%)	21 (20%)	14 (15%)		
Other	6 (4%)	11 (4%)	2 (2%)	2 (2%)		
β2 microglobulin at diagnosis (median mg/L; range)	*76 u/k* 4 (0.4-48.6)	*290 u/k* 3.75 (0-40)	*51 u/k* 4.3 (0.4, 48.6)	*89 u/k* 4.1 (0, 11.1)	.948	.848
Stage at diagnosis (Durie/Salmon)	*15 u/k*	*162 u/k*	*6 u/k*	*54 u/k*	.167	.452
I	23 (17%)	32 (18%)	15 (15%)	9 (17%)		
II	28 (21%)	54 (30%)	21 (21%)	15 (29%)		
III	82 (62%)	94 (52%)	64 (64%)	28 (54%)		
Time to first ASCT (range) months:	7 (3, 146)	8 (1, 125)	6 (3, 141)	9 (4, 100)	.006	.004
<6 mns	55 (37%)	78 (23%)	46 (43%)	23 (23%)		
6-12 mns	56 (38%)	148 (44%)	38 (36%)	43 (43%)		
>12 mns	37 (25%)	109 (33%)	22 (21%)	35 (35%)		
Length of remission post-first ASCT:					.001	.317
<12 mns	35 (24%)	148 (43%)	38 (36%)	33 (31%)		*(excluding*
12-18 mns	17 (11%)	61 (18%)	16 (15%)	14 (13%)		*>24 mns category-*
18-24 mns	19 (13%)	46 (13%)	10 (9%)	17 (16%)		*matching criterion)*
>24 mns	87 (52%)	87 (25%)	42 (40)	42 (40%)		
Status at first ASCT:	*6 u/k*				.303	-
CR	20 (14%)	64 (19%)	16 (15%)	16 (15%)		*(matching*
PR	91 (64%)	222 (65%)	75 (71%)	75 (71%)		*criterion)*
MR	10 (7%)	11 (3%)	2 (2%)	2 (2%)		
SD	5 (4%)	10 (3%)	3 (3%)	3 (3%)		
PD	16 (11%)	35 (10%)	10 (9%)	10 (9%)		
Year of first ASCT:					.001	-
1990-1993	23 (16%)	73 (21%)	15 (14%)	15 (14%)		*(matching*
1994-1997	75 (51%)	107 (31%)	45 (42%)	45 (42%)		*criterion)*
1998-2002	50 (34%)	162 (47%)	46 (43%)	46 (43%)		

u/k indicates unknown; mns, months; ASCT, autologous stem cell transplant; CCT, conventional chemotherapy; PD, progressive disease; SD, stable disease; MR, minimal response; CR, complete remission; PR, partial remission.

a second ASCT, the median age of the cohort overall and those selected for the case-matched analysis was 53 years (range: 26-75) and 54 years (range: 26-75), respectively. In patients who underwent a second ASCT, the median interval between diagnosis and first ASCT was 6 months (range: 3-141). For those who received CCT as salvage therapy, the median time from diagnosis to first ASCT was 9 months (range: 4-100). No significant difference in the time to relapse from first ASCT was demonstrated between the second ASCT and CCT cohorts (median 19 months [range: 3-106] vs 18 months [range: 4-80]; $P = .410$). In the second ASCT group, the use of TBI in the conditioning of the first ASCT did not affect the time to relapse: TBI (n = 11) means 17 months (95% confidence interval [CI] 11, 33) versus no TBI (n = 133), mean 25 months (95% CI 20, 30), $P = .31$ (Mann-Whitney test).

Nonrelapse Mortality (NRM)

At a median follow-up of 108 months (range: 8-174) for those who underwent a second ASCT as salvage therapy, 21 of 143 evaluable patients died of treatment-related causes. The 100-day NRM cumulative incidence for the total second ASCT (n = 148) and ASCT cohort used in the case-matched analysis (n = 106) were 8% (95% CI 4%-13%) and 7% (3%-14%). The cumulative incidence of NRM at 1 and 5 years for the second ASCT cohort was 7% (95% CI 3%-13%) and 12% (95% CI 7%-19%), respectively ($P < .0001$, Supplementary Figure 1). No factors were identified as associated with the NRM in a univariate. No treatment-related deaths were reported in the CCT cohort.

Response Rate, Durability of Response, and Survival

A complete remission (CR) rate of 26% (95% CI 19, 33) and partial remission (PR) rate of 37% (95% CI 29, 44) were reported in the total second ASCT cohort (n = 148), compared with a CR rate of 27% (95% CI 19, 36) and PR rate of 37% (95% CI 27, 45) in the case-matched analysis cohort (n = 106; total second

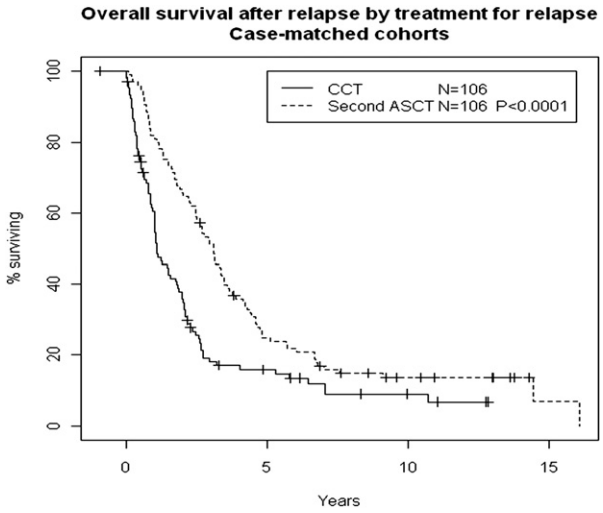

Figure 1. Cumulative incidence of NRM (Supplementary Figure 1) and overall survival for patients undergoing a second ASCT or CCT for relapsed MM.

ASCT vs matching cohort, $P = .66$) for the difference between the matched subset and the rest of the second transplantation group. In the case-matched cohort analysis, 182 patients have died (second ASCT n = 91, CCT n = 91), with a median time from first transplantation to death of 37 months for the second ASCT cohort and 13 months for the CCT cohort. The majority of patients died because of disease progression (n = 116), although 14 died of nonmyeloma-related causes. As such, there was a significant difference in the NRM between the second ASCT and CCT cohorts ($P = .001$). Thus, the 4-year relapse-associated mortality rate for the second ASCT cohort was 68% compared with 78% for the CCT cohort ($P = .0001$). The 4-year OS for those who underwent a second ASCT was 32% (95% CI 24%-45%) compared with 22% (95% CI 13%-35%) for those who underwent CCT alone at relapse ($P < .0001$; Figure 1B).

Parameters Influencing Survival Post-Salvage Therapy

Patient's age at first transplant predicts survival from relapse

Univariate analysis demonstrates that OS and PFS from first and second ASCT is superior in patients age <65 years at the time of their first ASCT, with a median OS from the second ASCT of 3.2 years (95% CI 2.4, 3.9) for those ≤54 years of age at first ASCT, 2.0 years (95% CI 1.4, 2.6) for those 55-65, and 0.8 years (95% CI 0.1, 1.9) for those >65 ($P < .0001$). For the comparative analysis, we examined the OS from relapse in each cohort. The median OS from relapse for patients age ≤54 years at first ASCT was 3.5 years (95% CI 2.7,4.6) in the second ASCT cohort and 1.75 years (95% CI 1.1, 2.1) in the CCT cohort, as illustrated in Figure 2A ($P = .0019$). In contrast, for patients age 55 to 65 years at first ASCT, the median OS was 2.7 years (95% CI 2.2, 3.4) in the second ASCT cohort and 1 year (95% CI 0.2,2.7) in the CCT cohort ($P = .0015$), with a median OS from relapse of 1.1 years (95% CI 0.1,3.4) and 0.7 years (95% CI 0.2,2.7) in the second ASCT and CCT cohorts, respectively, for those age >65 years at first ASCT ($P = .92$; Supplementary Figure 2).

β_2MG at diagnosis predicts survival from relapse

The level of β_2MG at diagnosis has previously been demonstrated to be a significant prognostic factor [14]. Therefore, we examined whether β_2MG at diagnosis could differentiate those who may perform better from a second ASCT as salvage therapy compared with CCT. A β_2MG <2.5 mg/L is associated with OS advantage whether a second ASCT or CCT is utilized as salvage therapy (Supplementary Figure 3), although no effect on PFS is demonstrated. However, this may be related to the lack of availability of β_2MG in more than half the study population.

Survival by duration of remission post-first transplant

It has been shown in previous studies that the duration of response to a first ASCT may predict for response to subsequent therapy, whether it be a second ASCT or CCT [13,15]. In a time-dependent regression analysis, the duration of first remission significantly affects the PFS ($P = .019$ for remission < 9 months, $P = .0006$ for remission >18 months; Figure 3A). Similarly, the time from first ASCT to

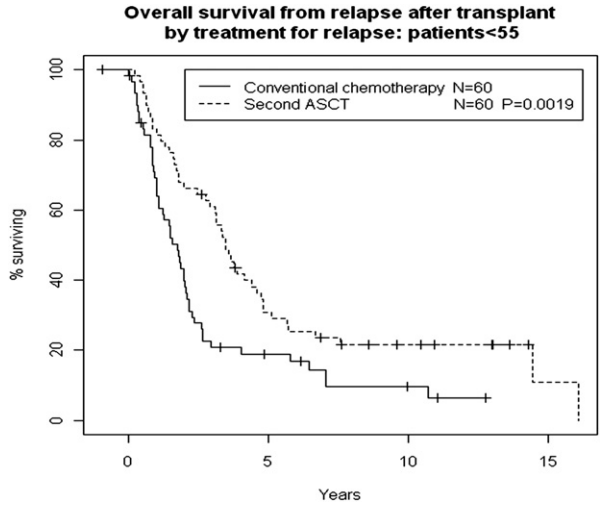

Figure 2. The effect of age at first ASCT on the overall survival from relapse in patients undergoing either a second ASCT or CCT (n = 106) as salvage therapy for relapsed MM. Patients age ≤54 years at first ASCT who received a second ASCT or CCT at relapse and those age 55 to 65 years and >65 years at first ASCT (Supplementary Figure 2).

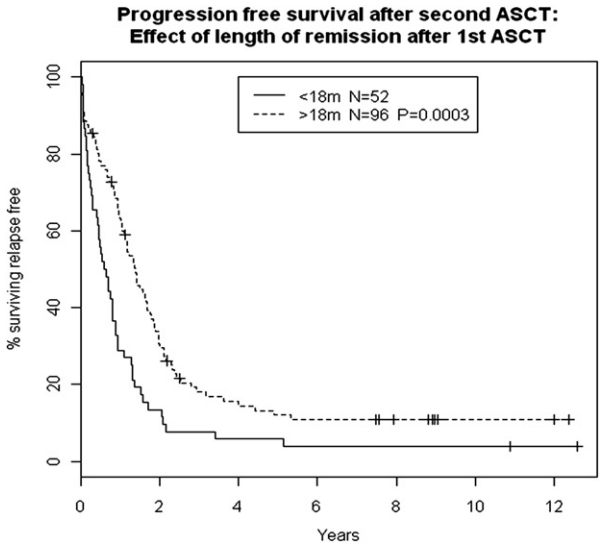

Figure 3. Time-dependent regression analysis of the effect of duration of response from first ASCT on PFS (A) and OS (Supplementary Figure 4) post-first ASCT and the effect of duration of response from first ASCT of >18 months on OS compared with CCT (Supplementary Figure 5).

relapse significantly affected OS, becoming significant after 9 months post-ASCT ($P = .001$) and increasing in significance beyond 18 months post-first ASCT ($P < .0002$; Supplementary Figure 4). When a second ASCT was compared with CCT as salvage therapy, a duration of response greater than 18 months post-first ASCT demonstrated a superior OS in patients receiving a second ASCT compared with CCT, with a median of 3.9 years (95% CI 3.1,4.8) versus 1.8 years (95% CI 1.1,2.3) ($P = .0011$), respectively (Supplementary Figure 5).

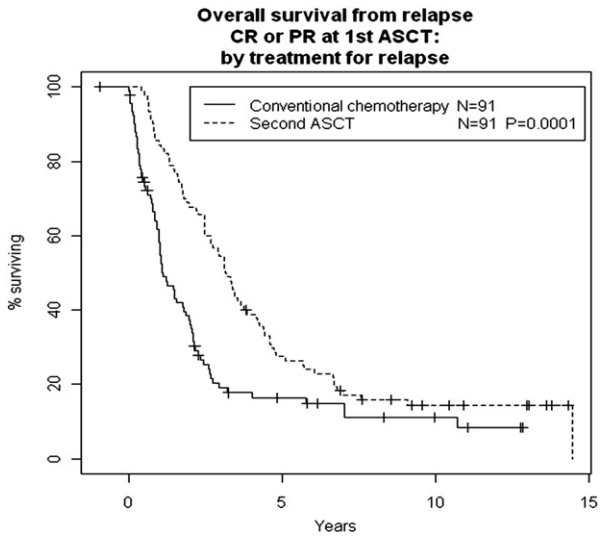

Figure 4. The effect of depth of response following a first ASCT on OS following salvage therapy for progressive disease: patients achieving a CR/PR, treated by second ASCT or CCT.

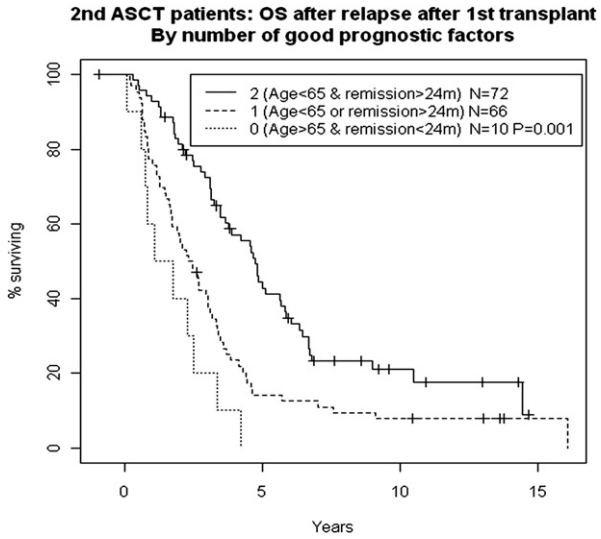

Figure 5. The combined effect of age at second ASCT and remission duration from first ASCT on 5-year OS.

Survival by disease status following an initial ASCT

The depth of response has been shown to predict improved PFS and OS, although the timing of such a response remains in debate [16-18]. We determined whether the depth of response following a first ASCT significantly affected the OS from relapse differentially in each treatment cohort (second ASCT vs CCT). In patients who achieved at least a PR (CR/PR) following a first ASCT, a second ASCT as salvage therapy demonstrated a superior OS (3.1 years [95% CI 2.5, 3.7] vs 1.1 years [95% CI 1.0, 1.8]; $P < .0001$) compared with those who received CCT (Figure 4). However, in patients with poorly responding disease to ASCT in first line, demonstrating no response, minimal response, or progressive disease, then no difference in OS (2.0 years [95% CI 0.2, 3.1] vs 1.0 years [95% CI 0.4, 2.0]; $P = .394$) was demonstrable, although this may relate to low patient numbers (n = 15).

Multivariate Analysis

To determine what parameters should be considered in treatment decision making for salvage therapy and whether to incorporate a second ASCT, we performed a multivariate regression analysis using the case-matched control pairings, to examine the independent influence of age at first ASCT, status at first ASCT, length of remission post-first ASCT, and year of transplantation (Supplementary Table 1). The OS and PFS of patients after second ASCT is significantly affected by the patient's age at second ASCT and the remission duration from first ASCT with β_2MG at diagnosis affecting OS only. We wished to provide a clinically relevant scoring system to assist

in decision making, and we examined the 5-year OS for patients score 0 (≥65 years, remission ≤24 months: n = 10), 1 (≤65 years or remission ≥24 months: n = 65) and 2 (≤65 years and remission ≥24 months: n = 72). The 5-year OS for score 0, 1, and 2 was 0%, 14%, and 43%, respectively ($P = .001$; Figure 5).

DISCUSSION

High-dose Melphalan supported by ASCT in first remission is currently accepted as gold standard consolidation for patients with MM deemed fit as first-line therapy. However, prolonged progression free survival post-ASCT is uncommon, and selection of optimal treatment for disease relapse is the major decision for patients and treating clinicians [12,13]. The role of planned second ASCT as initial therapy in MM has been studied prospectively in randomized trials and analysis from large registry studies [16,19,20]. A second, on-demand ASCT has been reported to be efficacious in patients with malignant lymphoma and Hodgkin's disease, associated with limited NRM and a PFS of 30% to 40% [21-23]. In the setting of relapsed MM, clinicians have opted for a second ASCT following reinduction therapy, but randomized controlled trial data or systematic outcome analysis in this setting is lacking [24,25]. As such, there is a lack of clear guidance and criteria for selection of patients who may benefit from this approach.

We present the outcomes of the large cohort of patients who underwent a second ASCT as salvage management of their relapsed MM following an initial ASCT with optimal follow-up, comparing these to a case-matched cohort. A second ASCT demonstrated superior relapse-associated mortality compared with CCT (68% vs 78%), associated with an improved OS (32% vs 22%) at 4 years. This compares favorably with previously published small studies in this setting, although these studies reported shorter follow-up [24-26]. To identify prognostic factors, we addressed key parameters that may influence the outcome of a second ASCT at relapse, including age at first transplantation, disease status at second ASCT, and time to relapse following the first ASCT. When time to relapse from the first ASCT is examined, the significance starts to emerge at 9 months from the first ASCT, although the significance increases with increasing interval between first ASCT and relapse. This finding is earlier than previous reports of salvage ASCT and the impact of time to relapse on survival where a significant benefit is reported at 12 to 18 months, and thus the data presented here provides the treating clinician with evidence to assist clinical decision making [26-29]. Age at second transplantation and β_2MG were both identified as significant independent prognostic factors, affecting both time to progression and OS. When taken together, the data assists in clinical decision making, indicating that those over the age of 65 with less than a 2-year remission from the first ASCT benefit the least from a second ASCT and should be considered for alternative consolidation strategies.

It is important to recognize the limitations of this retrospective study. First, the reinduction regimens, both pre-ASCT and in the CCT cohort, were heterogeneous, although, using defined response criteria, it was suitable to analyze and compare the study cohorts. Second, there were insufficient data on cytogenetic analysis and β_2MG at diagnosis and at relapse to permit confidence in a comparative analysis. These issues will be addressed in a UK randomized prospective study (NCRI Myeloma X study), which is currently recruiting.

Although the safety of a first ASCT has improved over recent years, concerns regarding the use of a second ASCT as salvage therapy may be raised, associating this procedure with increased toxicity and NRM. We demonstrated that the NRM was 7% (95% CI 3%-13%) and 12% (95% CI 7%-19%) at 1 and 5 years, similar to that reported in smaller studies [24,25]. However, it has been suggested that such patients may have a higher frequency of grade 3 and 4 toxicities including renal dysfunction [25].

In recent years novel agents such as Bortezomib, Thalidomide, and Lenalidomide have been introduced both for up-front and salvage therapy in MM [30]. Such therapies, in combination, have significantly increased the response rates of relapsed MM. Although the depth and rapidity of responses to Bortezomib-containing regimens are significant, with response rates in the range of 60% to 70%, the duration of responses remains disappointing in the salvage setting [31,32]. This has led several investigators to study the role of new drug combinations including Bortezomib and other, novel agents [33,34]. An alternative strategy is to use a second ASCT, shown here to have superiority over CCT in terms of PFS and OS, to augment the responses to novel agents. This is the strategy behind the current UK RCT in this setting where a Bortezomib combination as reinduction therapy is consolidated either with a low-dose alkylating regimen or a second ASCT, in progress (http://www.ukmf.org.uk/trials.htm).

Despite the recent advances in the treatment of MM, a second ASCT as salvage therapy could potentially add to the benefit of novel therapies in eligible patients. Although randomized control trial–derived data is lacking in this setting, the retrospective registry data analysis presented here can be employed to guide clinicians and patients to their therapeutic decisions incorporating a second ASCT for the treatment of relapsed disease. In summary, the data presented here offers clinically useful conclusions regarding the role and value of a second ASCT as salvage therapy for relapsed

MM. The availability of novel agents may improve further the disease responsiveness to a second ASCT rather than negate its usefulness in the salvage setting, by improving the depth of response pre-ASCT, which may result in improved durability of responses.

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AUTHORSHIP STATEMENT

Authorship was determined in accordance with the BSBMT Authorship policy (http://www.bsbmt.org/pages/46-CTC_Clinical_Trials_Committee). G.C. and K.K. designed the study and E.F., G.C., R.P., and K.K. analyzed the data. E.F. and G.C. wrote the article and K.K., G.J.M., F.E.D., S.K., M.P., J.A., N.R., and D.I.M. collected data, revised the article, and gave final approval. The authors report no conflicts of interest.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi: 10.1016/j.bbmt.2011.04.005.

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