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The impact of salvage autologous stem cell transplantion on overall survival in patients with relapsed multiple myeloma: Final results from the BSBMT/UKMF Myeloma X Relapse (Intensive) randomised open-label phase 3 trial.

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Summary

Background The Myeloma X trial previously reported improved durability of response (time to disease progression) in patients with relapsed multiple myeloma with salvage autologous stem cell transplantation (ASCT) compared to oral cyclophosphamide in patients with multiple myeloma relapsing after a first ASCT. We report the final overall survival results of the trial.

Methods BSBMT/UKMF Myeloma X was a multi-centre, phase 3, open-label randomised trial undertaken at 51 centres in the United Kingdom. Eligible patients with multiple myeloma relapsing after a prior ASCT were re-induced with intravenous bortezomib (1·3 mg/m^2 on days 1, 4, 8, 11), intravenous doxorubicin (9 mg/m^2/day on days 1-4) and oral dexamethasone (40 mg/day on days 1-4, 8-11, and 15-18 during cycle 1 and days 1-4 during cycles 2-4), with supportive care as per local institutional protocols before randomization in a 1:1 ratio to either high-dose melphalan (200 mg/m^2) and salvage ASCT or weekly oral cyclophosphamide (400mg/m^2 per week for 12 weeks). Randomisation was by permuted blocks stratified by length of first remission and response to re-induction therapy). The primary endpoint was time to disease progression; the study was also powered to detect a difference in the secondary endpoint, overall survival. Further secondary endpoints were response rate, progression-free survival, overall survival, toxicity and safety, pain and quality of life. Exploratory endpoints included time to second objective disease progression (PFS2). Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00747877 and European Clinical Trials Database, number 2006-005890-24 and is now in long-term follow-up.

Results Between 16 April 2008 and 19 November 2012, 297 patients were registered into the study and 174 randomised to receive either high-dose melphalan and salvage ASCT (n=89) or oral weekly cyclophosphamide (n=85). Median age was 61 years (IQR 55-65) with 74% of patients relapsing >24 months from first ASCT. Median follow-up at the date of analysis amongst randomised patients was 52 months (IQR 41–62) at which point 75 patients (43·1%) have died (31 in the salvage ASCT group and 44 in the oral weekly cyclophosphamide group). The median overall survival was superior in the salvage ASCT group compared with weekly

cyclophosphamide group (67 months [95% CI 55-∞] vs 52 months [95% CI 42-60]; logrank p=0·022; HR=0·56, [95% CI 0·35-0·90], p=0·0169). A reduced hazard of death in the salvage ASCT compared to weekly cyclophosphamide group was evident in patients achieving sCR/CR to re-induction therapy (HR 0·30 [95% CI 0·06–1·55]), and those without adverse risk *iFISH* (HR 0·33, [95% CI 0·14–0·80]). An updated analysis of time to disease progression and progression-free survival showed the superiority of salvage ASCT over weekly cyclophosphamide. PFS2 was superior in the salvage ASCT group compared with weekly cyclophosphamide (67 months [95% CI 52–∞] vs 35m [95% CI 31–43]; logrank p<0·0001). Following progression, 20 patients (of 85, 27%) in the weekly cyclophosphamide group underwent post-protocol salvage ASCT in third- or fourth-line treatment. The PFS2 in the weekly cyclophosphamide group split by subsequent-line salvage ASCT was not significantly different (logrank p= 0·269). Similarly, the overall survival in weekly cyclophosphamide groups split by subsequent-line salvage ASCT was not significantly different (logrank p=0·139). During extended follow-up, no further treatment-related or unrelated adverse events were reported. 15 SPMs were reported in 12 patients (7 in the salvage ASCT group and 5 in the oral weekly cyclophosphamide group). The cumulative incidence of second primary malignancies at 60 months after trial entry is 5·2% [95% CI 2.1%-8.2%]. Second primary malignancies were reported in 12 patients (7 in the salvage ASCT group and 5 in the oral weekly cyclophosphamide group). There was no significant difference between randomized groups in time to developing the first SPM (Pepe-Mori p=0·546).

Interpretation Salvage ASCT increases overall survival when consolidating re-induction therapy in patients with multiple myeloma at first relapse after a first ASCT. The delay of salvage ASCT to third-line or later may not confer the same degree of advantage as seen with salvage ASCT at first relapse.

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Introduction

The introduction of autologous stem cell transplantation (ASCT) to support high dose melphalan in patients with multiple myeloma (MM) in the 1980s represented a step change in the management of this disease, with randomised trials confirming its clinical utility over conventional chemotherapy in terms of progression-free and overall survival.[1-3] As a consequence, the procedure is considered standard of care for the treatment of patients with newly diagnosed MM generally up to the age of 65 to 70 years old without significant comorbidities.[4,5] The incorporation of novel agents (thalidomide, bortezomib and lenalidomide) into the first-line management strategy during induction, consolidation or maintenance, over the recent past has further contributed to improving patient outcomes.[6-9] However, for the vast majority of patients, cure remains elusive and the disease will eventually relapse. Due to recent advances, a host of options to manage relapsed disease exist without a standard treatment being clearly defined. Immunomodulatory drugs (IMiDs e.g. thalidomide, lenalidomide, pomalidomide), proteasome inhibitors (PIs e.g. bortezomib, carfilzomib, ixazomib) and monoclonal antibody immunotherapy (MoAb e.g. elotuzamab, daratumumab, isatuximab) offer new and exciting disease management strategies.[10]

ASCT is defined as salvage if the patient has already received a prior ASCT and undergoes salvage ASCT (sASCT) after evidence of disease progression, regardless of the number of lines of treatment administered after the first ASCT.[11] Salvage ASCT presents an appealing option because of the potential for long-term disease control and the relatively good tolerability of the procedure. Until recently, only retrospective, registry-based or single-centre analyses investigating the use of ASCT in the relapse setting after a prior ASCT have been published, which have all suggested a benefit for the repeated use of sASCT.[12-16] These analyses provide evidence of efficacy and acceptable toxicity in terms of transplant-related mortality associated with sASCT. Furthermore, when analysed for independent factors associated with improved durability of response, the duration of response to the first ASCT appears most important.[12,14]

We have recently published the results of the primary objective analysis from BSBMT/UKMF Myeloma X trial, a phase 3, randomised, multi-centre, open-label study that determined the role of a sASCT in providing superior durability of response after a bortezomib-based re-induction in patients with MM relapsing after a prior ASCT.[17] The results from this initial analysis have potential to alter clinical practice and have been a core element of the recently published international collaborative guidelines in this setting.[11] The key secondary endpoint of this randomized controlled trial (RCT) was to evaluate the impact of sASCT on overall survival (OS) of patients relapsing after a prior ASCT. Furthermore, we sought to evaluate the impact of sASCT on subsequent disease management using time to second objective disease progression (PFS2) and to delineate patient subgroups that may benefit the most from sASCT and in particular, to evaluate the impact of age and disease stage at re-treatment on outcomes.

Methods

Study design and patients

Patients with symptomatic, measurable MM were eligible if they required treatment for first progressive or relapsed disease (as defined by the International Myeloma Working Group criteria) at least 18 months after a prior ASCT (a trial amendment was submitted to allow this timeframe to be reduced to 12 months in 2011).[17] Patients with an immunofixation-negative response to first-line therapy, who became immunofixation-positive, had to demonstrate a >5g/l absolute increase in paraprotein to be eligible. Detailed inclusion and exclusion criteria have been previously described.[17] Patients were excluded if they had received therapy for their relapsed disease, had a poor performance score (ECOG Performance Status 3-4), grade 2 peripheral neuropathy, known resistance to PAD therapy (or elements contained within: bortezomib, doxorubicin and dexamethasone) and any comorbidity that would preclude ASCT. Symptomatic relapse (sRel) was defined as any one of: haemoglobin <110 g/L; calcium >2·6 μmol/L or creatinine >110 umol/L at trial registration and biochemical, asymptomatic relapse (aRel) defined as none of these criteria being met. All patients gave written informed consent. The study was approved by the national ethics review board (Multi-centre Research Ethics Committee, UK), institutional review boards of the participating centers, approved by the competent regulatory authority (Medicines and Healthcare Products Regulatory Agency, UK) and was conducted according to the Declaration of Helsinki and the principles of International Conference on Harmonization Guidelines for Good Clinical Practice. This randomised, multi-centre, open-label, parallel group phase 3 trial with an initial single intervention registration phase was conducted at 51 centres in the United Kingdom.

The trial procedures have been detailed in previous described.[17] In brief, re-induction therapy consisted of sequential cycles of the PAD regimen (intravenous bortezomib 1·3 mg/m^2 on days 1, 4, 8, 11; intravenous doxorubicin 9 mg/m^2/day on days 1-4; oral dexamethasone 40 mg/day on days 1-4, 8-11, and 15-18 during cycle 1 and days 1-4 during cycles 2-4), with supportive care as per local institutional protocols (aciclovir, cotrimoxazole and a proton-pump inhibitor).

Subsequently, 110 patients underwent peripheral blood stem cell (PBSC) re-mobilization and harvest.[18] Eligible patients were randomly assigned (in a 1:1 stratified randomization by length of first remission (<18, 18-24 and >24 months) and response to re-induction therapy) to receive consolidation therapy consisting either of intravenous melphalan 200 mg/m^2 followed by ASCT (sASCT) or non-transplant consolidation (weekly cyclophosphamide) consisting of oral cyclophosphamide at 400mg/m^2 per week for 12 weeks, as delineated in the trial CONSORT diagram (Appendix page 4).

The primary endpoint was time to progression of disease (TTP). Secondary endpoints were response rate, progression-free survival (PFS), overall survival (OS), toxicity and safety, pain and quality of life. Pain and quality of life results will be reported separately. Exploratory endpoints included time to second objective disease progression (PFS2), treatment-free interval and survival after progression. Response and disease progression were assessed according to the IMWG criteria for MM with external confirmation of response and disease progression by a central laboratory and independent clinical review of the central and local laboratory data. Time to progression was defined as the time from randomization to disease progression. Deaths not due primarily to disease progression were censored at time of death. PFS2 was defined as time from randomization to progression on next-line treatment, commencement of subsequent line treatment or death from any cause. OS was defined as the time from randomization to death from any cause and PFS was defined as the time from randomization to first documented assessment demonstrating disease progression or death from any cause.

Cytogenetic risk profiles were delineated using CD138$^+$ selected (Miltenyi AutoMac, Miltenyi-Biotec, Germany) bone marrow aspirate samples at trial registration and at disease progression. Interphase fluorescence *in situ* hybridisation (*iFISH*) was performed with commercial probes, using CD138-purified plasma cells to determine deletion of chromosome 17p (*TP53*), *IGH* and *MYC* gene rearrangements and for the presence of *FGFR3*/*IGH* [t(4;14)] and *MAF*/*IGH* [t(14;16)] fusion genes amongst other abnormalities. For the detection of a *TP53* deletion, a cut-off of 20% plasma cell involvement was used and for fusion gene detection the reporting was absolute (present

versus absent). An adverse risk cytogenetic profile was defined as the presence of any of the following: *FGFR3/IGH* [t(4;14)], *MAF/IGH* [t(14;16)] or *TP*53 deletion [del17p]. If none of these abnormalities were present, patients were defined as having standard risk disease.

Statistical analysis

Sample size and trial closure details have been described previously.[17] The trial closed to recruitment in November 2012 on the recommendation of the independent Leukaemia Trials Steering Committee following an interim analysis of the primary endpoint At this time, 297 patients had been registered and 174 randomized after approximately 4·25 years of recruitment. An event-driven analysis of overall survival was specified in the long-term follow-up statistical analysis plan to assess this key secondary endpoint when the trial population was more mature. It was hypothesized that a hazard ratio of 0·5 could be anticipated given the results of the final analysis of the primary endpoint. Assuming a minimum follow-up of 2 years for all randomized patients, 65 events would provide 80% power to detect this effect at a 5% level of significance.

The cut-off date for the long-term follow-up analysis was 14th July 2015 and all data entered into the database up to this time point was incorporated in the analysis. The intention-to-treat (ITT) population for the TTP, response rate, PFS, PFS2 and OS endpoints related to consolidation treatment (i.e. post-randomization) included all patients entering the randomization. The safety population consisted of all patients who received at least one dose of study treatment and was used for toxicity and safety endpoints. All statistical analyses were undertaken in SAS (version 9·4; SAS Institute, Cary, NC). Cox proportional hazards regression was used to analyze time-to-event endpoints adjusting for the stratification factors (length of first remission or plateau and response to PAD re-induction therapy), and in addition whether or not mobilization therapy was received. The proportional hazards assumptions were assessed by plotting the hazards over time for each treatment group. The Kaplan-Meier method was used to estimate survival functions and these were compared using the logrank test. Competing risks analysis was performed for the

primary endpoint (TTP), treating deaths without progression as competing events, using Fine-Gray regression.

Statistical Analysis Plan-defined subgroup analyses were carried out to assess whether the differences in TTP, PFS2 and OS by treatment group differed according to β_2-microglobulin at the time of registration, adverse cytogenetic risk groups (*iFISH*), and response to re-induction chemotherapy. Subgroup-analysis was undertaken using Cox proportional hazards regression model with appropriate interaction terms adjusting for the stratification and whether or not mobilization therapy was received. Likelihood ratio tests comparing nested models were used to test for treatment heterogeneity by subgroup. Statistical Analysis Plan-defined exploratory analyses were carried out to assess the effect of subsequent third- or fourth-line non-protocol sASCT on PFS2 and OS and the incidence of second primary malignancies (SPM) in population for all registered and all randomised patients. SPM incidence was estimated for all registered patients, alongside all randomised patients receiving treatment on trial, to identify any evidence of the risk of second malignancy from any trial treatment. Cumulative incidence functions were estimated by non-parametric maximum likelihood estimation. Cumulative incidence curves were compared using the Pepe-Mori test. This study is registered with ClinicalTrials.gov number: NCT00747877; EudraCT Number: 2006-005890-24.

Role of the funding source

The primary funder of the trial was Cancer Research UK [A7264] with financial contributions also received from Janssen-Cilag Ltd and Chugai Pharma UK. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The study was designed by Professor Gordon Cook and the Trial Management Group (TMG), on behalf of the United Kingdom Myeloma Forum (UKMF) and the British Society of Blood & Marrow Transplantation (BSBMT). Data collection and the final analysis were performed by the Clinical Trials Research Unit, University of Leeds. The TMG, chaired by Professor Cook, verified the accuracy and completeness of the data reported and the adherence of the study to the protocol, in

accordance with the principles of GCP. Professor Brown vouches for the statistical accuracy of the manuscript. The first author wrote the first draft of the manuscript, and made the decision to submit the manuscript for publication in agreement with all the investigators participating in the trial. All authors had full access to the data and reviewed and approved the manuscript before submission.

Results

Patients and treatment

Between 16 April 2008 and 19 November 2012, 297 patients were registered. A total of 293 of 297 registered patients received PAD induction therapy, of whom 281 had the protocol-defined 2-4 cycles and 55% (162 of 297) completed four cycles (Trial CONSORT diagram, Appendix page 4). A total of sixty-eight patients (of 297 registered 23%) were enrolled into the current study, who also had participated in the unrelated Myeloma IX trial, a study of treatment in newly diagnosed MM. Subsequently, 110 patients underwent PBSC re-mobilization[18] and 174 patients were randomly assigned to receive sASCT (n=89) or NTC (n=85). Baseline demographic and disease characteristics were well-balanced between the treatment groups (Table 1), except for a higher proportion of patients with International Staging System (ISS) III in the transplant group. The median age was 61 years (IQR 56-65 years). Patients were mostly bortezomib-naïve (280 of 297 registered patients 94%); induction prior to front-line ASCT was thalidomide-based in 61% of patients (182 of 297) with only 17% (50 of 297) having received thalidomide maintenance following the initial ASCT, as part of the Myeloma IX study. No patient had received lenalidomide as first-line therapy.

Cytogenetic data by *iFISH* at trial registration were available for 149 patients (50%) treated with PAD re-induction and for 88 (50%) of patients randomized to either salvage ASCT or weekly cyclophosphamide. Cytogenetic abnormalities were collated into a cytogenetic risk profile. This resulted in 13 (15%) randomized patients (sASCT n=7 and weekly cyclophosphamide n=6) having an adverse risk profile (defined by the presence of any one of the following: t(4;14), t(14;16) or

del17p) by *iFISH* and 75 patients (85·2%) having a standard risk profile (absence of adverse genetic risk factors, but including the presence of hyperdiploidy, t(11;14), del13q and *IGH* rearrangement with no defined translocation partner.

The median time from the primary myeloma diagnosis to randomization was 4·0 years (IQR 3·1–5·4). The median time from the previous ASCT to the first progression/relapse was 2·6 years (IQR 1·8–3·5) and to the first required re-treatment was 2·8 years (IQR 2·0–4·0). In pre-planned sub-groups, median time from first ASCT to first progression/relapse in aRel and sRel sub-groups was 2·5 (IQR 1·9-3·8) and 2·6 (IQR 1·9-3·6), respectively and between the age groups ≤65 and >65 years was 2.7 (IQR 1·9-3·9) and 2·4 (IQR 1·9-3·4), respectively. The reasons for not proceeding to randomization and the status of patients at trial closure have been described elsewhere[17] although the main reason for not proceeding was insufficient stem cells available for ASCT (34%, 41 of 123 registered patients).

In addition to the overall survival analysis, secondary endpoints included overall response rate after both re-induction and randomised treatment and the feasibility and impact of peripheral blood stem cell harvesting, which have now been published elsewhere.[17,18] These have been summarised in the Appendix (pages 11 and 12).

Relapse and Relapse management

At the cut-off date for the long-term follow-up analysis (July 14, 2015), median follow up was 52 months (IQR 41–62) in the whole randomised population: 50 months (IQR 37–62) in the sASCT group and 54 months (IQR 43–61) in the weekly cyclophosphamide group. There have been 146 disease progression events for the ITT population: sASCT group n=71 compared to n=75 in the weekly cyclophosphamide group. Updated TTP demonstrates continued advantage in the sASCT group compared to weekly cyclophosphamide (19 months [95% CI 16–26] vs. 11 months [95% CI 9–12]; logrank p<0·0001; Appendix page 5). Competing risks analysis of updated TTP, treating the 2 deaths reported without progression as competing events, showed the same advantage (Appendix, page 13) Similarly, updated PFS demonstrates continued advantage in the sASCT

group compared to weekly cyclophosphamide (19 months [95% CI 16–26] vs. 11 months [95% CI 9–12]; logrank p<0·0001; Appendix page 6).

To-date, following progression on protocol, 63 patients (89%) in the sASCT group and 63 patients (84%) in the weekly cyclophosphamide group have received third-line therapy, primarily consisting of a lenalidomide-based combination (56 patients (89%) in the sASCT and 51 patients (81%) in the weekly cyclophosphamide groups). Twenty patients (27%) in the weekly cyclophosphamide group underwent salvage ASCT in third- or fourth-line (weekly cyclophosphamide/sASCT), with 1 patient in each group proceeding to allogeneic SCT. Subsequent to this third-line therapy there have been 93 PFS2 events for the ITT population. In the sASCT group, 35 second progressions or deaths (39%) have been confirmed compared to 58 second progressions or deaths (68%) in the weekly cyclophosphamide group. The PFS2 was significantly prolonged in the sASCT compared with the weekly cyclophosphamide groups (sASCT: 67 [95% CI 52–∞] vs. weekly cyclophosphamide: 35m [95% CI 31–43]; logrank p<0·0001; Figure 1A), but PFS2 in weekly cyclophosphamide groups split by third- or fourth-line sASCT were not significantly different (weekly cyclophosphamide /sASCT: 31m [95% CI 23–42] vs. weekly cyclophosphamide 39m [95% CI 32–47]; logrank p= 0·269; Figure 1B). No significant impact of age at trial registration was identified in relation to PFS2 (≤65 years: HR=0.36 [95% CI 0.22–0.58]; >65 years: HR=0.53 [95% CI 0.21-1.34]; likelihood ratio test (LRT) p=0·827; Figure 1C & Appendix page 7) When the symptomatic status at relapse was considered, there was no significant difference in PFS2 in patients receiving treatment for biochemical relapse (aRel: HR=0.42 [95% CI 0.24–0.72]) compared to symptomatic relapse (sRel: HR=0.35 [95% CI 0.17–0.72]; LRT p=0·526; Figure 1C & Appendix, page 8). When the impact of randomized therapy was considered in patients who had no identified adverse cytogenetic features, there was no evidence of improved PFS2 in favour of the sASCT (standard: HR=0·30 [95% CI 0·14–0·65]; adverse: HR=0·47 [95% CI 0·08–2·89]; LRT p=0·097; Figure 1C).

Overall survival

At last follow up, 107 patients (36%) have died, with 32 patients having died prior to randomization and 75 patients (43%) having died after randomization (31 (of 84 35%) in the sASCT group and 44 (of 89 52%) in the weekly cyclophosphamide group). The main cause of death after randomization was progressive disease (63%) with all causes of death shown in Table 2. The 1-year non-relapse mortality remains 2·5% in the sASCT group and 0% in the weekly cyclophosphamide group. The median survival was 67 months (95% CI 55–∞) in the sASCT group compared with 52 months (95% CI 42–60) in the weekly cyclophosphamide group (logrank p=0·022; Figure 2A). Cox proportional hazards regression (adjusted for stratification factors and whether PBSC was remobilized) showed a reduced hazard of death in the sASCT group compared to NTC (HR=0·56, [95% CI 0·35–0.90], p=0·0169).

Consequent to relapsed disease management, a superior 4-year OS was observed with sASCT utilized in second line as compared to third line or not at all (sASCT: 69% [95% CI 58–79] vs weekly cyclophosphamide /sASCT: 61% [95% CI 52–69] vs NTC 50% [95% CI 36–64]). However, the OS in weekly cyclophosphamide groups split by subsequent line sASCT were not significantly different (logrank p= 0·139, Figure 2B).

When OS by randomized treatment is considered in relation to age (≤65 years vs. >65 years), no significant further benefit can be observed in either subgroup (≤65 years: HR=0·54 [95% CI 0·32–0·91]; >65 years: HR=0·75 [95% CI 0·27–2·12]; LRT p=0·635; Figure 2C and Appendix page 9). In terms of biochemical or asymptomatic (aRel) as opposed to symptomatic (sRel) relapse, there was also no significant benefit in treating aRel over sRel (aRel: HR=0·49 [95% CI 0·22–1·11]; sRel: HR=0·63 [95% CI 0·29–1·37]; LRT p=0·564; Figure 2C and Appendix page 10). sCR/CR response after re-induction therapy (sCR/CR: HR=0·30 [95% CI 0·06–1·55] vs. VGPR/PR: HR=0·64 [95% CI 0·35–1·20]; HR=0·68 [95% CI 0·35–1·20]; SD: HR=0·68 [95% CI 0·14–3·38]; LRT p=0·812; Figure 2C), ASCT1 TTP<24m (<24m: HR=0·42 [95% CI 0·17–1·05]; ≥24m: HR=0·62 [95% CI 0·31–1·24]; LRT p=0.857; Figure 2C) and β_2M concentration at trial registration <3·5mg/L (β_2M<3·5mg/L: HR=0·57 [95% CI 0·31–1·05]; β_2M≥3.5mg/L: HR=0·50 [95% CI 0·22–1·14]; LRT p = 0·955; Figure 2C) showed no significant further benefit in subgroup analysis. The absence of adverse risk *iFISH*

(standard: HR=0·33 [95% CI 0·14–0·80] vs. adverse: HR=0·93 [95% CI 0·13–6·63]; LRT p=0·058) showed no evidence of improved OS in favour of sASCT (Figure 2C).

Adverse events and second primary malignancies (SPM)

All patients who received at least one dose of study treatment were evaluated for adverse events, including SPM incidence. Since the primary endpoint report, no further treatment-related or unrelated adverse events were reported. Adverse events relating to re-induction and randomized treatments have previously been reported.[17] With a median follow-up for SPM of 39 months (IQR 25-54), 15 SPMs were reported in 12 patients (sASCT n=7; weekly cyclophosphamide n=5). The characteristics of reported SPMs is illustrated in Table 3 where the nature of SPMs appears similar between the randomized treatment groups. The median time to develop a SPM was 39·1 months (IQR 31·6-54·3), with a cumulative incidence of 5.2% [95% CI 2.1%-8.2%] at 60 months, as illustrated in Figure 3A. There was no significant difference between randomized treatments in terms of time to developing the first SPM (Pepe-Mori test p=0·546; Figure 3B). To date, 6 patients (50%) have died after being diagnosed with an SPM on trial and 1 patient death (8·3%) was reported as a consequence of the development of an SPM (secondary acute myeloid leukaemia after weekly cyclophosphamide).

Discussion

This multi-centre, phase 3 study evaluated the application of a sASCT in patients with disease recurrence following a previous ASCT for multiple myeloma and demonstrates a clear advantage in overall survival associated with sASCT. Though the clinical utility of a sASCT had been demonstrated to significantly prolonged TTP compared to non-transplant consolidation (weekly cyclophosphamide)[17], the impact on post-progression management and overall survival remained to be determined. Prior to this randomized controlled trial, the published retrospective experience indicated a clinical benefit supporting its use in practice[19]. In the prospective setting, the superior durability of response (TTP and PFS) associated with a sASCT in the Myeloma X study has been incorporated in clinical guidance through an international collaborative evidence review.[11] The data presented in the current manuscript, to our knowledge for the first time,

demonstrates clear evidence of improvement in survivorship when a sASCT is incorporated into the management pathway of patients relapsing after a prior ASCT. The choice of weekly cyclophosphamide as post-induction consolidation for the control group may be questioned in the current treatment landscape, however, there is no global standard of care for post re-induction consolidation and weekly cyclophosphamide is a standard of care in the UK following previous Medical Research Council trials demonstrating the utility in the non-transplant setting.

The impact of modern management on the survivorship of myeloma patients has been evident in several recently published works.[20-22] However demonstrating a survival benefit in a clinical interventional trial has become more complicated owing to the use of ever-increasing post-progression treatment options.[20,21,23] In this study, we demonstrate that the use of sASCT induces superior durability of disease control and is associated with an OS advantage, confirming recent retrospective analysis in the era of novel agents in the management of relapsed myeloma.[24] The question of timing of the sASCT is raised by the study design: is the incorporation of a sASCT in second- versus third-line therapeutic management differentially beneficial? The data analysed in this study indicates that the OS advantage of second line sASCT was maintained compared to when a sASCT was used in the third line setting, however there was a trend to improved OS when a sASCT was used in third line as opposed to not at all.

In the era of evolving novel therapies, continuous treatment delivery with newer agents are designed to improve durability of response and offer the potential of improved survivorship. Two key trials in the relapse setting, ASPIRE[25] and ELOQUENT 2[26], utilized carfilzomib and elotuzumab, respectively, on a backbone of lenalidomide and dexamethasone. The reported superior PFS in ELOQUENT 2 (19·4 months) with the triplet combination was similar to the PFS from our study, where continuous treatment was not delivered, though the reported PFS with the triplet regimen in the ASPIRE study was superior (26·3 months). Both studies reported their primary end points with limited follow-up to determine if these interventions had a significant impact on OS and thus making a direct comparison difficult with the current study. Notwithstanding, in the ASPIRE study, a median 2-year OS was reported as 73% in the triplet combination arm, whereas in this

study we report a 69% 4-year OS. This highlights that with limited exposure to a novel agent (bortezomib) consolidated with a single, non-continuous therapeutic intervention (sASCT), a durable period of disease control relates to a survival advantage with a significant treatment-free interval, and therefore a potential improvement in quality of life from treatment-related side effects for patients.

In MM studies, because patients receive treatment in temporally separated, but mutually interdependent episodes, there is a need to incorporate these issues in a suitable endpoint, such as PFS2, to determine if the intervention being tested does not have a deleterious impact on subsequent therapy outcomes, as well as OS.[27,28] In the current study, we demonstrate that the use of sASCT to consolidate re-induction therapy does not compromise the durability of response to subsequent, post-trial therapy, but in fact could enhance this, in association with an overall survival advantage. What is more is we demonstrate that sASCT at first relapse demonstrates a clear advantage in PFS2 durability over patients receiving sASCT at second relapse, suggesting that sASCT should be performed at first relapse to maximize the survivorship from relapsed myeloma after a prior ASCT.

Pre-defined subgroup analysis in myeloma trials is key to understanding which patient may benefit the most from the trial intervention, an important feature given the heterogeneity of myeloma. Though much research attention has focused on the molecular aberrations, a greater understanding of the heterogeneity of the host biology also plays a role.[29-32] Whilst age did not impact on outcomes, important for real-world clinical practice, it is worthy of note that good performance status (ECOG ≤2) at trial registration and randomization were per protocol requirements. Finally, the effect of managing biochemical (asymptomatic: aRel) versus symptomatic (sRel) relapse was tested in our analysis as to-date there is very little published prospective data to inform the practicing clinician, with expert opinion to serve as the only guidance.[33,34] The sub-group analysis in this study suggests an advantage in terms of PFS2 and OS when patients with aRel are re-induced and consolidated with a sASCT. In the light of this result

it becomes important to design a trial to specifically answer this question both in the arena of sASCT and for those patients deemed unfit for ASCT.

This study design highlights several issues that require further attention. Firstly, the trial design incorporating a PI-based re-induction regimen rather than an IMiD-based regimen reflected not only the high level of IMiD exposure in first line for trial registrants but also the healthcare system restriction of access to treatment. It is worthy of note, that only 68 (23%) of the trial entrants, and 48 (28%) of the trial randomised patients, were previously enrolled into the (unrelated) CRUK-funded Myeloma IX study[35], which incorporated a randomisation to thalidomide maintenance this explaining the low level of trial participants who progress on a maintenance strategy prior to entry into this study. Though offering a dataset on which to base clinical decision-making, the role of sASCT in the setting of IMiD or combined IMiD and PI usage remains to be clarified. Secondly, the role of post-sASCT consolidation and maintenance has not been addressed. Several studies have demonstrated the clinical utility of consolidation/maintenance in prolonging PFS, and in some studies also OS, but these have all been conducted in first line with no available data to inform their role in the sASCT setting.[7-9] Both these issues will be addressed in the forthcoming UK Myeloma Research Alliance (UKMRA) Myeloma XII study (EudraCT Number: 2016-000905-35).

The last issue is long-term safety following the delivery of a second high dose melphalan exposure. The on-trial treatment safety and toxicity profile has been previously reported[17], and here we provide further information on the safety of sASCT in relation to SPM. Recently, SPM following ASCT and maintenance (particularly lenalidomide) strategies have been raised as an issue in front line therapy.[36,37] In our study, we did not see an increased risk from SPM when a sASCT was performed, compared to weekly cyclophosphamide. Nonetheless, it would be complacent to ignore this as a potential long-term complication, especially given that SPM may well increase in importance in the future as we strive towards improved survival from myeloma. Currently, the cumulative risk of death due to SPM is outweighed by the risk from myeloma though for a patient who develops a SPM, the outcome is of great importance. Data regarding survival in myeloma

patients with SPMs is limited though a recent population-based analysis reveals an especially poor survival of myeloma patients developing MDS/AML, irrespective of their exposure to high dose melphalan.[38]

In conclusion, the long-term follow-up of this prospective, randomized study demonstrates the superiority of a salvage ASCT in consolidating the response obtained from novel agent re-induction therapy in terms of overall survival. The clear demonstration of impact on survivorship in the relapse setting provides further evidence for salvage ASCT to be considered a standard of care for eligible patients, although this approach to the clinical management of relapsed myeloma is already widely practiced in many countries. We have demonstrated that the superiority of salvage ASCT was beneficial irrespective of the quality of response to re-induction, the level of β_2-microglobulin, and the response duration to the initial ASCT although there clearly remains an issue of best clinical management in patients with genetic high-risk disease. The role of post-transplant consolidation and maintenance remains to be clarified in this setting. This study offers the evidence for informed decision-making regarding the choice of ASCT for clinicians and patients alike and will have an important impact on global clinical practice impact.

Words: 4402

Panel: Research in context

Evidence before this study.

The management of relapsed disease following a prior autologous stem cell transplant (ASCT) has evolved with the advent of novel agent-containing strategies. In this setting, salvage ASCT (sASCT) has been utilised in routine clinical practice, though the evidence-base is somewhat limited, especially in relationship to survivorship. A systematic review (PubMed search on the following terms: salvage autologous transplant, second autologous transplant, relapsed myeloma) in 2016 demonstrated 24 published studies that were suitable for consideration. The literature reviews demonstrated that the published evidence to support sASCT was based on retrospective registry or single centre studies only, primarily without the incorporation of novel agents in the re-induction phase. These have suggested that sASCT provides a benefit in terms of progression-free survival and in some studies, overall survival, compared to conventional chemotherapy combinations. As the published results were limited by their retrospective and non-comparative nature, as well as largely being conducted in an era where novel anti-myeloma agents were not available, there was a clear need for prospective, randomised, multi-centre data that delineates the true potential for sASCT.

Added value of this study.

BSBMT/UKMF Myeloma X is the only prospective interventional study in this setting and has previously reported a superior durability durability of response (TTP & PFS) when a sASCT is used. At the time of reporting, the impact on survivorship was not possible. Therefore, follow-up analysis of secondary trial endpoints are key to provide the longer-term setting of the impact of sASCT. We show that a sASCT administered at first relapse for myeloma significantly improves duration of response to next treatment (PFS2) and overall survival (OS). This provides the first randomised evidence to suggest a survivorship benefit for sASCT with no significant influence being inferred by β2-microglobulin at relapse and age, in particular. Adverse cytogenetic risk markers continue to show poorer response, in terms of response duration.

Implications of all the available evidence.

The data provides the necessary prospective evidence not only substantiating the previous retrospective studies in an up-to-date clinical treatment scenario but demonstrating the clinical utility of a sASCT in first relapsed myeloma. Given the nature of this trial and the derived results, we believe this study will formulate clinical practice in many healthcare systems, setting a standard of clinical care in myeloma. The results of this study have already been incorporated into national (NICE) as well as international (IMWG) guidelines with evidence demonstrating real-world increase in sASCT utilisation (BSBMT and EBMT registries). Taken together, the results or this study are already having an impact on the clinical management pathway in myeloma and aid in the decision-making process for both physicians and myeloma patients.

Contributors

Authorship was determined in accordance with the UK Myeloma Research Alliance authorship policy, ratified by the Trial Management Group policy delineated in the protocol. GC designed the study and GC, DAC, JMB & TCMM analysed the data. GC wrote the article and AJA, CW, JMB, DAC, JC, JAS, CP, KY, JC, HH, JB, AH, GP, SC, EH, SOC, MTD & TCMM collected data, revised the article and gave final approval.

Conflicts of interest

GC: Janssen, Celgene, Takeda, Sanofi, BMS - Honoraria, Research Funding, Speakers Bureau; AJA: Amgen, Celgene, Janssesn – Consultancy, Research; CDW: Janssen, Celgene, Amgen, Takeda - Honoraria and Speakers Bureau; JAS: MSD, Janssen, Celgene, Sanofi - Consultancy, Educational support , Speakers Bureau; JC: Celgene, Janssen - Research Funding and Speakers Bureau; CP: Janssen, Celgene - Speakers Bureau; EH: Celgene, Janssen - Speakers Bureau, Consultancy; SOC: Celgene - Research Funding; KY: Amgen, Novartis, Takeda, BMS, Janssen- Honoraria, Consultancy; JMB: Janssen, Celgene, Amgen, Pfizer -Educational support, Speakers Bureau, Consultancy; JMB: Janssen, Roche, Celgene, Bayer- Research Funding; TCMM: Janssen, Celgene - Meeting support

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Table 1: Demographic and baseline characteristics of the intention-to-treat population

	Registration (n=297)	**Salvage ASCT (n=89)**	weekly cyclophosphamide **(n=85)**
Age			
Median – yr	61	61	61
Range – yr	38–75	40–73	40–73
Sex – no. (%)			
Male	208 (70)	65 (73)	61 (72)
Female	89 (30)	24 (27)	24 (28)
Ethnicity – no. (%)			
White	267 (89·9)	81 (91·0)	80 (94·1)
Asian	7 (2·3)	3 (3·3)	2 (2·4)
Afro-Caribbean	13 (4·4)	3 (3·6)	2 (2·4)
Other	4 (1·4)	0	0
International Staging System stage* – no. (%)			
I	88 (29·6)	24 (27)	31 (36·5)
II	93 (31·3)	24 (27)	27 (31·8)
III	38 (12·8)	16 (18)	8 (9·4)
Missing	78 (26·3)	25 (28·1)	19 (22·4)
Isotype – no. (%)			
IgG	190 (64·0)	60 (67·4)	57 (67·1)
IgA	55 (18·5)	13 (14·6)	18 (21·2)
LC	26 (9·4)	7 (7·9)	7 (8·2)
IgM/IgD	3 (1·0)	1 (1·1)	1 (1·2)
Non-secretory	9 (3·0)	3 (3·4)	2 (2·4)
Symptomatic status			
sRel	60 (48·8)	36 (40·4)	38 (44·7)
aRel	63 (51·2)	53 (59·6)	47 (55·3)
TTP post ASCT1 – months	-		
< 18		3 (3·4)	2 (2·4)
18–24		22 (24·7)	19 (22·4)
> 24		64 (71·9)	64 (75·3)
Cytogenetic features – no.(%)**			
t(4;14)	14 (9·4)	5 (11·6)	3 (7·0)
t(11;14)	15 (10·1)	3 (7·0)	4 (9·5)
t(14;16)	3 (2·0)	0	2 (4·8)
Deletion 17p	11 (7·4)	4 (9·3)	1 (2·4)
Hyperdiploidy	20 (13·4)	4 (9·3)	6 (14·3)
Missing data/not tested	148	46	40

*Higher stages indicate more severe disease.

**Percentage expressed as the proportion detected amongst those tested

Table 2: Cause of death for all patients in the intention-to-treat population

	Pre-randomisation (n=32)	Salvage ASCT (n=31)	weekly cyclophosphamide (n=44)
Primary cause of death progressive disease			
Yes	19 (59·4%)	19 (61·3%)	28 (63·6%)
No	13 (40·6%)	12 (38·7%)	15 (34·1%)
Missing	0 (0·0%)	0 (0·0%)	1 (2·3%)
Other primary cause of death			
Infection, unspecified	9 (28·1%)		
Infection, respiratory tract	1 (3·1%)	0 (0·0%)	5 (11·5%)
Cerebro-vascular Accident	3 (9·3%)	1 (3·2%	2 (5·5%)
Intestinal Infarction		0 (0·0%)	1 (2·3%)
Spontaneous Thrombocytopenic Haemorrhage		0 (0·0%)	1 (2·3%)
Hypertensive disease		0 (0·0%)	1 (2·3%)
Second Primary Malignancy			
MDS		1 (3·2%)	0 (0·0%)
AML		0 (0·0%)	1 (2·3%)
Treatment-related death	1 (3·1%)		
Unknown		10 (32·2%)	5 (11·4%)

Table 3: Second Primary Malignancies occurring during protocol treatment for the safety population.

	weekly cyclophosphamide n=85	**Median time to onset (months, range)**	**sASCT (n=89)**	**Median time to onset (months, range)**
NMSC	5 (5·9%)	29 (17, 40)	1 (1·1%)	41
MSC	0	-	2 (2·2%)	26 (15, 51)
Solid Tumour	1 (1·2%)	37	1 (1·1%)	15
Hematologic	2 (2·4%)	33.5 (28, 39)	3 (3·3%)	39 (34, 71)
TOTAL	8 (9·4%)	33.5 (17, 40)	7 (7·9%)	39 (15, 71)

Key: **NMSC** – non-malignant skin cancer, **MSC** – melanomatous skin cancer

FIGURE LEGENDS

Figure 1. The impact of first relapse management on time to second progression or death from any cause (PFS2) (A) by randomized therapy, (B) by randomized therapy with the NTC group separated by those who later received sASCT after subsequent disease progression as part of third- or fourth-line therapy (weekly cyclophosphamide /sASCT) and not (weekly cyclophosphamide) and (C) forest plot of sub-group analysis performed for PFS2 using Cox proportional hazards regression. P(het.) refers to likelihood ratio test (LRT) evaluating heterogeneity of treatment effect between subgroups.

Figure 2. The impact of first relapse management on overall survival (OS) (A) by randomized therapy, (B) by randomized therapy with the weekly cyclophosphamide group separated by those who later received sASCT after subsequent disease progression as part of third- or fourth-line therapy (weekly cyclophosphamide /sASCT) and not (weekly cyclophosphamide) and (C) forest plot of sub-group analysis performed for OS using Cox proportional hazards regression. P(het.) refers to likelihood ratio test (LRT) evaluating heterogeneity of treatment effect between subgroups.

Figure 3. The cumulative incidence of time-to-first second primary malignancy in (A) the whole study group and (B) by randomized therapy.

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