High-dose chemotherapy plus autologous stem-cell transplantation as consolidation therapy in patients with relapsed multiple myeloma after previous autologous stem-cell transplantation (NCRI Myeloma X Relapse [Intensive trial]): a randomised, open-label, phase 3 trial

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See Comment page 786

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Summary

Background Relapsed multiple myeloma has no standard treatment, and the role of autologous stem-cell transplantation (ASCT) has not been fully defined. We aimed to compare high-dose melphalan plus salvage ASCT with cyclophosphamide in patients with relapsed multiple myeloma who had previously undergone ASCT.

Methods This multicentre, randomised, open-label, phase 3 study recruited patients aged at least 18 years with multiple myeloma who needed treatment for first progressive or relapsed disease at least 18 months after a previous ASCT from 51 centres across the UK. Before randomisation, eligible patients received bortezomib, doxorubicin, and dexamethasone (PAD) induction therapy and then underwent peripheral blood stem-cell mobilisation and harvesting if applicable. Eligible patients (with adequate stem-cell harvest) were randomly assigned (1:1), using an automated telephone randomisation line, to either high-dose melphalan 200 mg/m^2 plus salvage ASCT or oral cyclophosphamide (400mg/m^2 per week for 12 weeks). Randomisation was stratified by length of first remission or plateau and response to PAD re-induction therapy. The primary endpoint was time to disease progression, analysed by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00747877, and EudraCT, number 2006-005890-24.

Findings Between April 16, 2008, and Nov 19, 2012, 297 patients were registered, of whom 293 received PAD re-induction therapy. Between Aug 26, 2008, and Nov 16, 2012, 174 patients with sufficient PBSCs were randomised to salvage ASCT (n=89) or cyclophosphamide (n=85). After a median follow-up of 31 months (IQR 19–42), median time to progression was significantly longer in the salvage ASCT than in the cyclophosphamide group (19 months [95% CI 16–25] *vs* 11 months [9–12]; hazard ratio 0·36 [95% CI 0·25–0·53]; p<0·0001). Frequently reported (in >10% of patients) grade 3–4 adverse events with PAD induction, salvage ASCT, and cyclophosphamide were: neutropenia (125 [43%] of 293 patients after PAD, and 63 [76%] of 83 patients in the salvage ASCT group *vs* 11 [13%] of 84 patients in the cyclophosphamide group), thrombocytopenia (150 [51%] after PAD, and 60 [72%] *vs* four [5%], respectively), and peripheral neuropathy (35 [12%] after PAD, and none *vs* none, respectively).

Interpretation This study provides evidence for the improved efficacy of high-dose melphalan plus salvage ASCT when compared with cyclophosphamide in patients with relapsed multiple myeloma eligible for intensive therapy, which might help to guide clinical decisions regarding the management of such patients.

Funding Cancer Research UK.

Introduction

The introduction of autologous stem-cell transplantation (ASCT) for multiple myeloma in the 1980s marked a breakthrough in the management of this B-cell malignancy. Results of randomised trials comparing high-dose therapy plus ASCT with conventional chemotherapy have shown that transplantation improves progression-free and overall survival.[1,2] As a result, the procedure is regarded as the standard of care for patients with newly diagnosed multiple myeloma up to about age 65–70 years without substantial comorbidities.[3–5] The incorporation of thalidomide, bortezomib, and lenalidomide into the first-line management strategy during induction, consolidation, or maintenance therapy has further improved patient outcomes.[6–13] However, for most patients, a cure remains elusive and the disease will eventually relapse. Because of recent advances, many options to manage disease relapse exist, but no standard treatment has been clearly defined. Thalidomide, bortezomib, and lenalidomide form the mainstay of treatment in combination with steroids and conventional chemotherapy.

The use of ASCT at relapse (salvage ASCT) is an appealing option because of the potential for long-term

disease control and the reasonably good tolerability of the procedure. Results of several retrospective, registry-based or single-centre analyses investigating the use of salvage ASCT in the relapse setting after a previous ASCT have been published, and all suggest a benefit for the repeated use of the procedure.[14–21] A review[22] of available retrospective studies suggests that salvage ASCT can lead to objective responses in about 65% of patients, with progression-free survival and overall survival reaching 12 months and 32 months, respectively. Furthermore, using ASCT in the relapse setting seems to be associated with an overall treatment-related mortality of less than 5%.[14] Analyses to identify reasons for the success of salvage ASCT suggest that the duration of response to the first ASCT is crucial.[14–21] Taken together, these analyses point to an important role for salvage ASCT; however, until now, a prospective assessment had not been done.

On behalf of the UK Myeloma Forum and the British Society of Blood and Marrow Transplantation, we designed the National Cancer Research Institute Myeloma X Relapse (Intensive) trial to compare high-dose melphalan plus salvage ASCT with cyclophosphamide in patients with relapsed multiple myeloma who had previously undergone ASCT in the first-line setting. The choice of cyclophosphamide as post-induction consolidation for patients in the control group represented an accepted standard of care in the absence of a global standard of care in this setting.

Methods

Study design and patients

In this randomised, multicentre, open-label, parallel-group, phase 3 trial with an initial single-intervention registration phase, we recruited patients with symptomatic, measurable multiple myeloma from 51 National Health Service hospitals in England, Wales, Scotland, and Northern Ireland. Patients were eligible for registration if they needed treatment for first progressive or relapsed disease at least 18 months after a previous ASCT (reduced to 12 months in 2011 after the publication of expected benefit[14]); needed therapy for relapsed disease (as defined by the International Myeloma Working Group [IMWG] criteria[23]); were deemed fit by the treating physician to undergo an intensive therapeutic protocol; and were older than 18 years (no predetermined upper age limit). Patients who had a complete (immunofixation-negative) response to first-line therapy but who subsequently became immunofixation-positive had to have a greater than 5 g/L absolute increase in paraprotein to be eligible. Laboratory assessments to establish trial-entry eligibility were done within 14 days of registration, with the following tolerance limits: adequate full blood count (platelet count 350×10^9 cells per L and absolute neutrophil count 331×10^9 cells per L); adequate renal function (creatinine clearance 330 mL/min); adequate hepatobiliary function (total bilirubin <2×upper limit of normal [ULN] and an aspartate aminotransferase–alanine aminotransferase ratio of <2·5×ULN); adequate pulmonary function (no evidence of a history of pulmonary disease, and carbon monoxide transfer coefficient or diffusing capacity of the lung for carbon monoxide of ≥50%); and adequate cardiac function within 12 weeks before registration (left ventricular ejection fraction ≥40%).

Patients were excluded if they had received therapy for their relapsed disease, had an Eastern Cooperative Oncology Group performance status of 3–4, grade 2 peripheral neuropathy, known resistance to combined bortezomib, doxorubicin, and dexamethasone (PAD) therapy, or any comorbidity that would preclude high-dose chemotherapy.

All patients gave written informed consent. The study was approved by the national ethics review board (Multicentre Research Ethics Committee, UK), institutional review boards of the participating centres, and the competent regulatory authority (Medicines and Healthcare Products Regulatory Agency, UK), and was undertaken according to the Declaration of Helsinki and the principles of Good Clinical Practice as espoused in the Medicines for Human Use (Clinical Trials) Regulations. The trial management group, chaired by GC, verified the accuracy and completeness of the data reported and the adherence of the study to the protocol, and JMB vouches for the statistical accuracy of the manuscript.

Pre-randomisation procedures

Before randomisation, all eligible patients received re-induction chemotherapy, which consisted of intravenous bortezomib 1·3 mg/m² per day on days 1, 4, 8, and 11, intravenous doxorubicin 9 mg/m² per day on days 1–4, and oral dexamethasone 40 mg per day on days 1–4, 8–11, and 15–18 during cycle 1 and days 1–4 during cycles 2–4 (PAD). The delivery of intravenous doxorubicin was mainly a 4-day infusion, as per protocol, although bolus daily injection was permissible. Patients received supportive care as per local institutional protocols, although patients were recommended to receive aciclovir, co-trimoxazole, and a proton-pump inhibitor. Patients were eligible to progress to next stage if they had received 2–4 cycles of PAD re-induction chemotherapy according to the protocol and had a complete response, partial response, or stable disease following re-induction chemotherapy.

Patients then underwent peripheral blood stem cell (PBSC) mobilisation and harvesting; however, if sufficient PBSCs were available from their first-line ASCT, this procedure was not compulsory. Patients were eligible for randomisation if they had adequate stem-cell mobilisation (defined as $\geq2\times10^6$ CD34+ cells per kg or $\geq2\times10^8$ peripheral-blood mononuclear cells per kg) available for transplantation, including cells stored from a previous harvest; met all the laboratory-assessment

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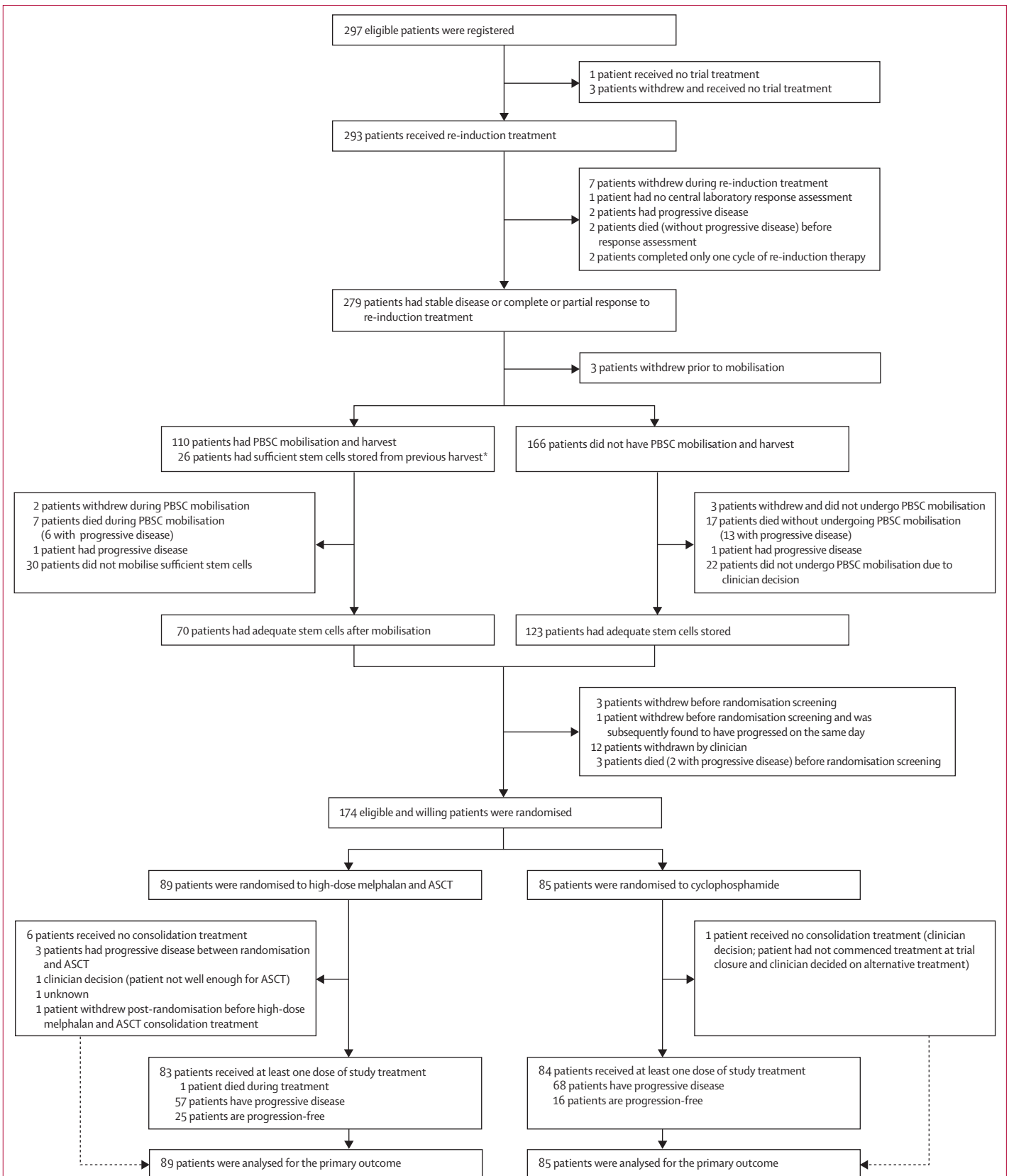
See Online for appendix


297 eligible patients were registered
1 patient received no trial treatment
3 patients withdrew and received no trial treatment
293 patients received re-induction treatment
7 patients withdrew during re-induction treatment
1 patient had no central laboratory response assessment
2 patients had progressive disease
2 patients died (without progressive disease) before response assessment
2 patients completed only one cycle of re-induction therapy
279 patients had stable disease or complete or partial response to re-induction treatment
3 patients withdrew prior to mobilisation
110 patients had PBSC mobilisation and harvest
26 patients had sufficient stem cells stored from previous harvest*
166 patients did not have PBSC mobilisation and harvest
2 patients withdrew during PBSC mobilisation
7 patients died during PBSC mobilisation (6 with progressive disease)
1 patient had progressive disease
30 patients did not mobilise sufficient stem cells
3 patients withdrew and did not undergo PBSC mobilisation
17 patients died without undergoing PBSC mobilisation (13 with progressive disease)
1 patient had progressive disease
22 patients did not undergo PBSC mobilisation due to clinician decision
70 patients had adequate stem cells after mobilisation
123 patients had adequate stem cells stored
3 patients withdrew before randomisation screening
1 patient withdrew before randomisation screening and was subsequently found to have progressed on the same day
12 patients withdrawn by clinician
3 patients died (2 with progressive disease) before randomisation screening
174 eligible and willing patients were randomised
89 patients were randomised to high-dose melphalan and ASCT
85 patients were randomised to cyclophosphamide
6 patients received no consolidation treatment
3 patients had progressive disease between randomisation and ASCT
1 clinician decision (patient not well enough for ASCT)
1 unknown
1 patient withdrew post-randomisation before high-dose melphalan and ASCT consolidation treatment
1 patient received no consolidation treatment (clinician decision; patient had not commenced treatment at trial closure and clinician decided on alternative treatment)
83 patients received at least one dose of study treatment
1 patient died during treatment
57 patients have progressive disease
25 patients are progression-free
84 patients received at least one dose of study treatment
68 patients have progressive disease
16 patients are progression-free
89 patients were analysed for the primary outcome
85 patients were analysed for the primary outcome

inclusion criteria for registration as described previously; and had no clinical evidence of deterioration in cardiac function since registration. They were excluded if progressive disease was detected.

Randomisation and masking

Eligible patients were randomly assigned on a 1:1 basis to receive either high-dose melphalan plus salvage ASCT or cyclophosphamide. A stratified permuted block randomisation was used to ensure treatment groups were well balanced for length of first remission or plateau (<18 months *vs* 18–24 months *vs* >24 months) and response to PAD re-induction therapy (stable disease *vs* partial or complete response). Randomisation was done centrally at the Clinical Trials Research Unit (Leeds, UK) using a 24-h automated telephone randomisation line according to randomisation lists produced by the trial statistician under the supervision of JMB. Due to the nature of the treatment, participants and those administering the interventions were aware of the treatment allocation. Assessment of outcomes was also unblinded, apart from final confirmation of central response and progression, which was done by an independent myeloma physician masked to treatment allocation.

Procedures

Patients received consolidation therapy consisting of a single infusion of intravenous melphalan 200 mg/m² followed by ASCT after 24–48 h, or oral cyclophosphamide 400 mg/m² per week for 12 weeks.

Response and disease progression were assessed according to the IMWG uniform response criteria for multiple myeloma (appendix) using blood and urine samples, unless progression of myeloma occurred as an isolated bone lesion, growth of a plasmacytoma, or an increase in plasma cells in the bone marrow without a change in M-protein, in which case tissue histological examination was done. Response and disease progression were confirmed by a central laboratory using sequential samples of blood and urine and bone marrow aspirates taken at baseline, after re-induction treatment, 100 days after ASCT or 30 days after the end of cyclophosphamide treatment, every year after randomisation, and at disease progression. Patients were followed up by the treating physician more frequently than annually, varying according to local practice. Central lab review was done every year. Central response and progression were then finally confirmed by central review (by an independent myeloma physician masked to treatment allocation) of the central laboratory data (when available) and local laboratory data, including serological (both paraprotein concentrations and serum free light-chain assays) and morphological (bone marrow assessment) responses. The response and time of progression were defined using the IMWG criteria, as per protocol.

Bone marrow aspirate samples at trial entry and at disease progression were CD138+ selected (autoMACS, Miltenyi Biotec, Cologne, Germany) and plasma cell

***Figure 1*: Trial profile**
ASCT=autologous stem-cell transplant. PBSC=peripheral blood stem cell. *The 26 patients who had sufficient stem cells stored still underwent PBSC mobilisation and harvest.

	Registered patients (n=297)	Randomly assigned patients (n=174)	
		Melphalan plus ASCT (n=89)	Cyclophosphamide (n=85)
Age (years)	61 (38–75)	61 (40–73)	61 (40–73)
Sex			
Male	208 (70%)	65 (73%)	61 (72%)
Female	89 (30%)	24 (27%)	24 (28%)
Ethnic origin*			
White	267 (90%)	81 (91%)	80 (94%)
Asian	7 (2%)	3 (3%)	2 (2%)
Afro-Caribbean	13 (4%)	3 (4%)	2 (2%)
Other	4 (1%)	0	0
ISS stage†			
I	88 (30%)	24 (27%)	31 (36%)
II	93 (31%)	24 (27%)	27 (32%)
III	38 (13%)	16 (18%)	8 (9%)
Missing	78 (26%)	25 (28%)	19 (22%)
Isotype*			
IgG	190 (64%)	60 (67%)	57 (67%)
IgA	55 (19%)	13 (15%)	18 (21%)
Light-chain deposition disease	26 (9%)	7 (8%)	7 (8%)
IgM/IgD	3 (1%)	1 (1%)	1 (1%)
Non-secretory myeloma	9 (3%)	3 (3%)	2 (2%)
TTP after first ASCT (months)			
<18	..	3 (3%)	2 (2%)
18–24	..	22 (25%)	19 (22%)
>24	..	64 (72%)	64 (75%)
Cytogenetic analysis			
Patients with available data	149 (50%)§	43 (48%)§	45 (53%)§
Cytogenetic features‡			
t(4;14)	14 (9%)	5 (12%)	3 (7%)
t(11;14)	15 (10%)	3 (7%)	4 (9%)
t(14;16)	3 (2%)	0	2 (4%)
Deletion 17p	11 (7%)	4 (9%)	1 (2%)
Deletion 13q	58 (39%)	21 (49%)	17 (38%)
Hyperdiploidy	20 (13%)	4 (9%)	6 (13%)
Cytogenetic risk group‡			
Adverse	24 (16%)	7 (16%)	6 (13%)
Standard	125 (84%)	36 (84%)	39 (87%)

Data are n (%) or median (range), unless otherwise indicated. TTP=time to progression. ASCT=autologous stem-cell transplant. ISS=International Staging System for multiple myeloma. *Data were missing or not stated for some participants. †Higher stages indicate more severe disease. ‡Percentages expressed as a proportion of patients for whom cytogenetic analysis data were available. §Numbers of patients in each of the rows do not add up to the number of patients with available data because some had no defect detected.

***Table 1*: Demographic and baseline characteristics of registered patients and randomly assigned patients, per treatment group**

suspensions were fixed in Carnoy's solution and stored at –20°C. Interphase fluorescence in-situ hybridisation (iFISH), was done with commercial probes, scored and image-captured using an AxioPlan microscope (Zeiss, Jena, Germany) with MetaSystems Isis software (Altlußheim, Germany). CD138-purified plasma cells were tested with probes to identify deletion of chromosome 17p, *TP53* [ch17p deletion], *IGH*, and *MYC* gene rearrangements, and for the presence of *FGFR3*/*IGH* [t(4;14)] and *MAF*/*IGH* [t(14;16)] fusion genes, among other abnormalities. For the detection of a *TP53* deletion, a cutoff of 20% plasma-cell involvement was used, and for fusion gene detection the reporting was absolute (present *vs* absent). An adverse risk cytogenetic profile was defined as the presence of *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.

Outcomes

The primary endpoint was time to progression of disease. Secondary endpoints were objective response, progression-free survival, overall survival, toxicity and safety, pain, and quality of life. Time to progression was measured from randomisation to the first assessment showing progressive disease. Overall survival was defined as the time from randomisation to death from any cause, and progression-free survival was defined as the time from randomisation to first documented assessment showing disease progression or death from any cause. Deaths not mainly due to disease progression were censored for the primary endpoint. We determined response in accordance with IMWG criteria.[23] Toxicity and safety were assessed after each cycle of protocol treatment according to adverse events, graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 during routine clinical assessments at each centre.[24] Pain and quality-of-life results will be reported separately.

Statistical analysis

We planned to register 460 patients with the aim of randomly assigning 320 to a treatment group. The sample size was based on a 4-year recruitment period and 2-year follow-up, 80% power, a 5% significance level, and a median time to progression of 14 months in the cyclophosphamide group to detect a 30% reduction in hazard ratio [HR] in the ASCT group compared with the cyclophosphamide group, equating to a 6-month improvement in median time to progression. On the basis of these assumptions, which we based on published retrospective study outcomes and an early phase trial of bortezomib in a similar population,[25] 249 events were required. We allowed for 5% of patients to drop out.

The trial closed to recruitment in November, 2012, after an interim analysis of the primary endpoint done at the request of the independent Medical Research Council Leukaemia Data Monitoring and Ethics Committee (DMEC) showed that the prespecified boundary (defined as a guideline as $p<0·001$) representing "overwhelming evidence" had been met. The DMEC reviewed all the information that they requested about statistical significance and the estimated treatment effects to come to a decision, and on the basis of the DMEC review, the chair of the Leukaemia Trials Steering Committee recommended that the trial be closed and the results unmasked. Centres were instructed to complete treatment as per protocol for those patients receiving treatment, and attending physicians were to administer treatment at their discretion to patients not yet receiving treatment. Follow-up data is being obtained regarding the nature of the treatments that were given to patients who had progressive disease after the trial closed, and durability of responses to this next line of therapy.

The cutoff date for the final analysis was July 9, 2013, and all data entered into the database up to that timepoint were incorporated in the final analysis. All registered patients were included in the analysis of objective response after PAD re-induction therapy. Time to progression, objective response, progression-free survival, and overall survival endpoints related to consolidation treatment (ie, after randomisation) were analysed in all patients who were randomly assigned to a treatment group. Toxicity and safety endpoints were assessed in the safety population, which consisted of all patients who received at least one dose of study treatment.

We used Cox regression to analyse time to progression, accounting for stratification factors (length of first remission or plateau and response to PAD re-induction therapy) and whether or not mobilisation therapy was received. We assessed the proportional hazards assumptions by plotting the hazards over time for each treatment group. We did similar analyses for overall survival and progression-free survival.

We did exploratory subgroup analyses for duration of response to PAD. Response rates (appendix) were compared with ordinal logistic regression analysis accounting for the stratification factors and whether or not mobilisation therapy was received.

We did sensitivity analyses to account for deviations from trial protocol for patients who had not completed study treatment at the time of trial closure by censoring these patients at the time of closure. All statistical analyses were done with SAS (version 9.2).

This study is registered with ClinicalTrials.gov, number NCT00747877 and with EudraCT, number 2006-005890-24.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to the data and reviewed and approved the manuscript before submission.

GC had final responsibility for the decision to submit for publication in agreement with all the investigators participating in the trial.

Results

Between April 16, 2008, and Nov 19, 2012, 297 patients were registered (figure 1). 293 (99%) of 297 registered patients received 967 cycles of PAD induction chemotherapy, of whom 281 (96%) had the protocol-defined two to four cycles and 162 (55%) completed four cycles. Participants who had enough stem cells did not need to remobilise; remobilisation was attempted in only 110 (37%) patients (figure 1). 26 (88%) patients had sufficient stem cells stored but still underwent PBSC mobilisation and harvest (figure 1). 166 (56%) patients did not undergo PBSC mobilisation and harvest, of whom 123 (74%) had sufficient stem cells stored. Between Aug 26, 2008, and Nov 16, 2012, 174 patients with newly mobilised PBSCs or sufficient PBSCs stored from their first transplant (or both) were randomly assigned to receive high-dose melphalan followed by ASCT (n=89) or oral cyclophosphamide (n=85; figure 1).

Baseline demographic and disease characteristics were well balanced between the treatment groups (table 1), except that a higher proportion of patients had International Staging System (ISS) stage 3 multiple myeloma in the ASCT group than in the cyclophosphamide group. The median age of all randomly assigned patients was 61 years (range 40–73). 280 (94%) of 297 registered patients were bortezomib-naive; induction therapy before first-line ASCT had consisted of thalidomide-based combinations in 182 (61%) of 297 patients and vincristine plus doxorubicin plus dexamethasone-like combinations in 84 (28%), with only 50 (17%) having received thalidomide maintenance after the initial transplant. No patients had received lenalidomide as a first-line therapy.

Cytogenetic data by iFISH at trial registration were available for 149 (50%) of 297 registered patients and for 88 (51%) of 174 randomly assigned patients (table 1). Cytogenetic abnormalities were collated into a cytogenetic risk profile, which resulted in 13 (15%) randomly assigned patients (table 1) having an adverse risk profile (defined by the presence of any one of the following: t[4;14], t[14;16], or del17p) and 75 (85%) randomly assigned patients 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 original myeloma diagnosis to randomisation was 4·1 years (range 2·2–13·6) in the salvage ASCT group and 3·7 years (2·4–13·2) in the

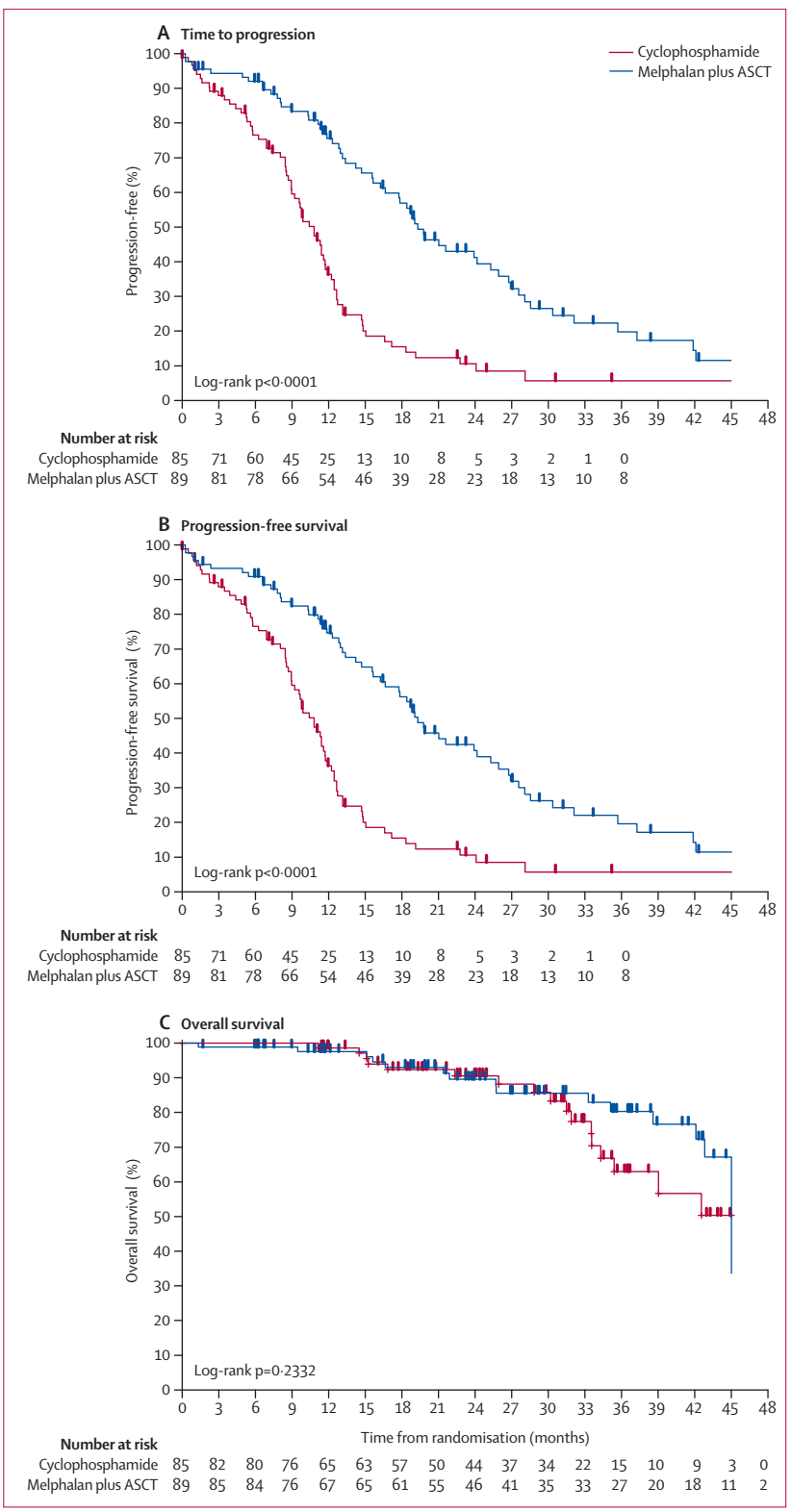


***Figure 2*: Progression and survival outcomes in the intention-to-treat population**

Kaplan-Meier curves were plotted for time to progression (A), defined as time from randomisation to the first assessment showing disease progression (deaths not due to disease progression were censored); progression-free survival (B), defined as time from randomisation to first assessment showing disease progression or death from any cause; and overall survival (C), defined as the time from randomisation to death from any cause. ASCT=autologous stem-cell transplant.

cyclophosphamide group. The median time from previous ASCT to first progression or relapse was 2·7 years (range 1·0–12·4) in the salvage ASCT group and 2·5 years (0·7–6·5) in the cyclophosphamide group and the median time from the previous ASCT to the first required treatment (ie, PAD induction therapy) was 2·8 years (range 1·1–12·4) in the salvage ASCT group and 2·6 years (1·2–8·3) in the cyclophosphamide group. Finally, the median time from registration to randomisation was 3·8 years (range 1·6–9·7) in the salvage ASCT group and 3·6 years (1·6–7·4) in the cyclophosphamide group. The reasons for registered patients not proceeding to randomisation, and the status of patients at trial closure, are summarised in the appendix.

At the cutoff date for the final analysis (July 9, 2013), the median follow-up was 31 months (IQR 19–42) in the whole population: 34 months (IQR 19–48) in the salvage ASCT group and 23 months (25–31) in the cyclophosphamide group. At data cutoff, 125 progression events had occurred in the intention-to-treat population (57 [64%] of 89 patients in the salvage ASCT group had confirmed disease progression *vs* 68 [80%] of 85 patients in the cyclophosphamide group). Time to progression was significantly longer in the salvage ASCT group than in the cyclophosphamide group (median 19 months [95% CI 16–25] *vs* 11 months [9–12]; HR 0·36 [95% CI 0·25–0·53]; p<0·0001; figure 2). ASCT also significantly extended progression-free survival compared with cyclophosphamide (median 19 months [95% CI 16–25] *vs* 11 months [9–11]; p<0·0001; figure 2).

At last follow-up, 61 (21%) of all 297 registered patients had died, with 29 patients having died before randomisation and 32 patients having died since randomisation (15 [17%] of 89 patients in the salvage ASCT group *vs* 17 [20%] of 85 patients in the cyclophosphamide group). Overall survival did not differ significantly between randomised groups (HR 0·62 [95% CI 0·3–1·27]; p value for treatment effect in the Cox proportional hazards regression model=0·19). Median overall survival has not been reached in either group. 3-year overall survival was 80·3% (95% CI 69·3–91·2) in the salvage ASCT group and 62·9% (46·6–79·2) in the cyclophosphamide group (figure 2). One (1%) patient in the salvage ASCT group and none in the cyclophosphamide group died from non-relapse mortality. The main causes of death in randomised patients were progressive disease (in eight [9%] of 89 patients in the salvage ASCT group *vs* nine [11%] of 85 patients in the cyclophosphamide group), peripheral vascular disease (none *vs* one [1%]), myelodysplastic syndrome (one [1%] *vs* none), pneumonia (none *vs* one [1%]), haemorrhage (none *vs* one [1%]), and subarachnoid haemorrhage (none *vs* one [1%]). Cause of death was not reported in six [7%] patients in the salvage ASCT group and four [5%] patients in the cyclophosphamide group.

After PAD induction therapy, 49 (16%; 95% CI 12·5–21·2) of 297 patients achieved a stringent complete response or complete response, 186 (63%; 56·9–68·2) had a very good partial response or partial response, and 44 (15%; 11·0–19·4) had stable disease (table 2). Thus, the proportion of patients achieving a very good partial response or better was 37% (111 of 297; 31·9–42·9), and the proportion of patients achieving an overall response was 79% (74·5–83·7; table 2). After randomisation, a stringent complete response or complete response was reported in 35 (39%; 95% CI 29·1–50·3) of 89 patients in the salvage ASCT group compared with 19 (22%; 14·3–32·7) of 85 patients in the cyclophosphamide group (odds ratio [OR] 2·24, 1·11–4·65; p=0·021). 39 (44%; 33·5–54·1) patients in the salvage ASCT group and 45 (53%; 42·3–63·6) in the cyclophosphamide group had a very good partial response or partial response. The proportion of patients with a very good partial response or better was 60% (53 of 89; 49·4–69·7) after salvage ASCT versus 47% (40 of 85; 36·4–57·7) after cyclophosphamide (OR 0·38, 95% CI 0·2–0·7; p=0·0036).

An analysis of responses to initial and salvage ASCT revealed that the proportion of patients who achieved an objective response after first-line ASCT was 96% (85 of 89), whereas it was 83% (74 of 89) after salvage ASCT. Of the 52 (58%) of 89 patients who achieved a stringent complete response or complete response after first-line ASCT, 28 (54%) reached a stringent complete response or complete response after salvage ASCT, whereas 15 (29%) achieved a very good partial response or partial response (appendix). Additionally, of the 33 (37%) of 89 patients who had a very good partial response or partial response after first-line ASCT, five (15%) achieved a stringent complete response or complete response after salvage ASCT, whereas 22 (67%) achieved a very good partial response or partial response.

	Response after PAD induction (n=297)	Response after randomised treatment (n=174)	
		Melphalan plus ASCT (n=89)	Cyclophosphamide (n=85)
Overall response	235 (79%)	74 (83%)	64 (75%)
Stringent complete response	23 (8%)	35 (39%)*	19 (22%)*
Complete response	26 (9%)	NA	NA
Very good partial response	62 (21%)	18 (20%)	21 (25%)
Partial response	124 (42%)	21 (24%)	24 (28%)
Stable disease	44 (15%)	4 (4%)	2 (2%)
Progressive disease	2 (<1%)	2 (2%)	15 (18%)
Early death†	2 (<1%)	1 (1%)	0
Response could not be assessed	10 (3%)	2 (2%)	3 (4%)

Patients missing from the table received no treatment. PAD=bortezomib, doxorubicin, and dexamethasone. ASCT=autologous stem-cell transplant. NA=not applicable. *Includes both stringent complete response and complete response. †Early death after PAD induction was defined as death between registration and up to and including 21 days after the final cycle of PAD commenced; early death after randomised treatment was defined as death between randomisation and up to and including 100 days after randomisation.

***Table 2*: Best response in all registered patients after PAD induction, and in all randomly assigned patients after randomised treatment**

The time-to-progression benefit associated with salvage ASCT was consistent across subgroups of patients defined by response to PAD re-induction therapy and β2-microglobulin concentration at registration, but not for those with an adverse cytogenetic risk by iFISH (figure 3). Additionally, time to progression was significantly longer in the salvage ASCT group than in the cyclophosphamide group when analysed by duration of response to the first-line ASCT. For the 64 (72%) of 89 patients in the salvage ASCT group and 64 (75%) of 85 in the cyclophosphamide group who had a first response lasting longer than 24 months, median time to progression was 24 months (95% CI 18–27) versus 11 months (10–12), respectively (HR 0·35, 95% CI 0·22–0·54; p<0·0001 from Cox proportional hazards regression model). For the 25 (28%) patients in the salvage ASCT group and 21 (25%) in the cyclophosphamide group who had a first response of 24 months or less, median time to progression was 13 months (95% CI 10–20) and 9 months (8–12), respectively (HR 0·37, 95% CI 0·19–0·74; p<0·0037 from Cox proportional hazards regression model).

Results of sensitivity analyses for time to progression, progression-free survival, and overall survival that censored patients who had not completed study treatment at the time of trial closure were similar to those of the intention-to-treat analyses (data not shown).

All patients who received at least one dose of study treatment were assessed for adverse events. During PAD induction therapy, 131 (45%) of 293 patients reported at least one serious adverse event, with 120 (60%) of 131 reported serious adverse events suspected to be related to the study medication. The most frequent CTCAE grade 3–4 adverse events were haematological (table 3): 125 (43%) of 293 patients who had PAD induction therapy had grade 3–4 neutropenia, and 150 (51%) had grade 3–4 thrombocytopenia, whereas grade 3–4 neuropathy (sensory plus motor) occurred in 35 (12%) patients. Gastrointestinal grade 3–4 toxicity was infrequent during PAD induction therapy (28 [10%] of 293 patients), as were grade 3–4 infections (25 [9%] patients). During induction, 184 (63%) of patients had a treatment delay, most frequently around cycle 3, which occurred in 101 (34%), mainly due to cytopenias. 154 (52%) of 293 patients needed a dose modification, with G-CSF support being administered to 49 (16%) patients to support PAD therapy, most frequently in cycle 4 (n=22 needed G-CSF support in cycle 4).

167 patients received the randomly assigned consolidation therapy (83 in the ASCT group and 84 in the cyclophosphamide group). The dose of intravenous melphalan was reduced from 200 mg/m² to 140 mg/m² in two (2%) patients owing to reduced creatinine clearance and in four (5%) patients for other reasons. A greater proportion of patients in the melphalan plus ASCT group than in the cyclophosphamide group had grade 3–4 adverse events related to neutropenia (63 [76%] of 83 in the melphalan plus ASCT group *vs* 11 [13%] of 84 in the cyclophosphamide group), thrombocytopenia (60 [72%] *vs* four [5%]), anaemia (19 [23%] *vs* one [1%]), diarrhoea (ten [12%] *vs* one [1%]), and nausea or vomiting (ten [12%] *vs* two [2%]; table 3). Second primary malignancies were reported in three patients at a median of 33·4 months (range 19·9–38·3) after trial registration: one patient was diagnosed with prostatic cancer in the ASCT group, with one patient diagnosed with squamous-cell cancer and one patient diagnosed with breast cancer in the cyclophosphamide group.

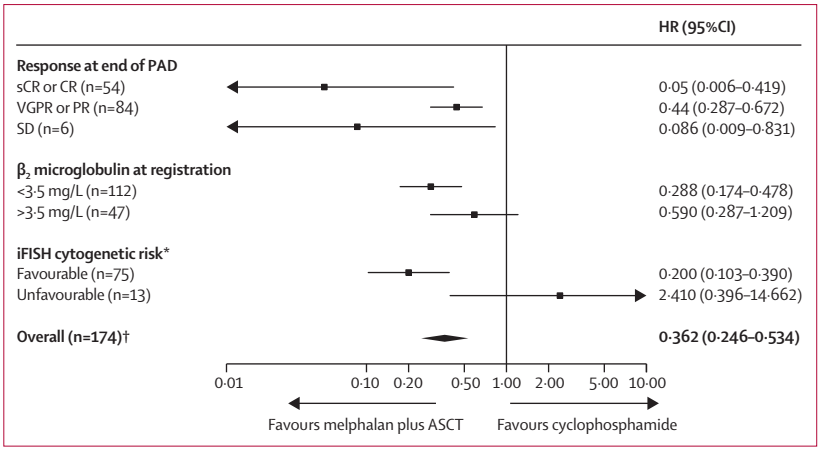


***Figure 3*: Subgroup analysis of time to progression**
HRs for risk of disease progression in the melphalan plus salvage ASCT group compared with the cyclophosphamide group. PAD=bortezomib, doxorubicin, and dexamethasone. sCR=stringent complete response. CR=complete response. VGPR=very good partial response. PR=partial response. iFISH=interphase fluorescence in-situ hybridisation. HR=hazard ratio. *Adverse risk was defined by the presence of a *t*(4;14) translocation, *t*(14;16) translocation, or *TP53* deletion; standard risk was defined by the absence of adverse markers. †Numbers for each subgroup do not add up to 174 overall because not all patients had the information needed for the subgroup analysis.

Discussion

This phase 3 study, which was stopped early because it crossed a stopping boundary for efficacy at an interim analysis, assessed the application of salvage ASCT in patients with recurrence of multiple myeloma after previous ASCT. The use of high-dose melphalan plus ASCT at relapse significantly prolonged time to progression compared with cyclophosphamide therapy.

Until now, only retrospective single-centre and registry studies had examined the role of salvage ASCT, all concluding a beneficial effect, although with varied results for durability of response (panel).[14–21] Our randomised study provides clear evidence for the benefit of high-dose melphalan plus salvage ASCT by showing that patients assigned to this treatment achieved a durable response after re-induction therapy with bortezomib, doxorubicin, and dexamethasone. No standard of care exists in the relapse setting, and patients typically receive combination therapy, including thalidomide, bortezomib, and lenalidomide. Few phase 3 trials have focused on treatment for first relapse in multiple myeloma, and although cross-trial comparisons are problematic, our results compare favourably with those achieved with combination therapy incorporating novel

(biological) agents. In one phase 3 trial,[26] time to progression after the triple combination of bortezomib, thalidomide, and dexamethasone (VTD) was 19·5 months in patients who had relapsed after first-line ASCT, and the proportion of patients who received VTD who were alive at 2 years was 71%. The durability of response in our trial was measured from randomisation, which occurred at a median of 3·8 months after treatment was initiated for progressive disease. In our study, 80·3% of patients in the salvage ASCT group were alive at 3 years compared with 62·9% in the cyclophosphamide group.

	PAD induction (n=293)	PBSC mobilisation (n=110)	Consolidation (n=167)	
			Melphalan plus ASCT (n=83)	Cyclophosphamide (n=84)
Neutropenia				
Grade 1–2	90 (31%)	14 (13%)	8 (10%)	34 (40%)
Grade 3	80 (27%)	6 (5%)	2 (2%)	10 (12%)
Grade 4	45 (15%)	18 (16%)	61 (73%)	1 (1%)
Thrombocytopenia				
Grade 1–2	90 (31%)	27 (25%)	3 (4%)	19 (23%)
Grade 3	75 (26%)	11 (10%)	6 (7%)	2 (2%)
Grade 4	75 (26%)	8 (7%)	54 (65%)	2 (2%)
Anaemia				
Grade 1–2	209 (71%)	0	46 (55%)	40 (48%)
Grade 3	19 (6%)	0	17 (20%)	1 (1%)
Grade 4	3 (1%)	0	2 (2%)	0
Infection				
Grade 1–2	3 (1%)	6 (5%)	1 (1%)	0
Grade 3	25 (9%)	9 (8%)	3 (4%)	0
Grade 4	0	0	0	0
Diarrhoea				
Grade 1–2	82 (28%)	0	47 (57%)	4 (5%)
Grade 3	12 (4%)	0	10 (12%)	1 (1%)
Grade 4	3 (1%)	0	0	0
Nausea				
Grade 1–2	109 (37%)	16 (15%)	46 (55%)	39 (46%)
Grade 3	6 (2%)	3 (3%)	7 (8%)	1 (1%)
Grade 4	1 (<1%)	0	0	0
Vomiting				
Grade 1–2	51 (17%)	7 (6%)	35 (42%)	14 (17%)
Grade 3	5 (2%)	3 (3%)	3 (3%)	1 (1%)
Grade 4	1 (<1%)	0	0	0
Sensory neuropathy				
Grade 1–2	151 (52%)	25 (23%)	0	0
Grade 3	27 (9%)	7 (6%)	0	0
Grade 4	3 (1%)	0	0	0
Motor neuropathy				
Grade 1–2	22 (8%)	0	0	0
Grade 3	5 (2%)	0	0	0
Grade 4	0	0	0	0

Data are n (%) of patients who had adverse events at that grade over all cycles of that stage of protocol treatment. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. The safety population consisted of all patients who received at least one dose of study treatment. No grade 5 events were reported. PAD=bortezomib, doxorubicin, and dexamethasone. PBSC=peripheral blood stem cell. ASCT=autologous stem-cell transplant.

Table 3: **Adverse events occurring during protocol treatment in the safety population**

Results of the predefined subgroup analysis in our study suggested that melphalan plus salvage ASCT was better than weekly cyclophosphamide, irrespective of the quality of response to PAD re-induction and the concentration of β_2-microglobulin at registration. Furthermore, melphalan plus salvage ASCT was better than weekly cyclophosphamide irrespective of the response duration to the initial ASCT, although time to progression seemed to be longer in patients with a response lasting longer than 24 months after their first ASCT than in those with a response of 24 months or less. High-dose melphalan plus salvage ASCT was not better than cyclophosphamide in patients with an adverse cytogenetic risk profile by iFISH. However, the small number of patients with an adverse cytogenetic risk profile makes the interpretation of this result difficult; therefore, we cannot firmly recommend that salvage ASCT should be avoided in patients with adverse cytogenetics at first relapse.

Randomised controlled trials that are stopped early for efficacy have been suggested to overestimate the effect size.[27] However, when a stringent and predefined stopping rule is in place[28] and greater than 50% of the required events have been reported,[29] stopping early has been suggested to have a negligible impact on estimated effect sizes. This study had a planned interim analysis included in the protocol with an appropriate stopping rule. This interim analysis was subsequently brought forward at the request of the independent DMEC, but a stringent ad-hoc rule was included for early interim analyses as described above and in the statistical analysis plan. The primary endpoint analysis was undertaken when 125 (50%) of the required 249 events had been reported, suggesting that the estimated effect could be at most minimally inflated.

Although salvage ASCT also extended progression-free survival compared with cyclophosphamide, as yet, overall survival does not significantly differ between the treatment groups. However, the current median follow-up is not sufficiently long enough to confidently assess the effect of salvage therapy on survival. The effect of therapy after progression, particularly because the trial closed early, might confound the survival analysis, especially if a significant proportion of patients in the cyclophosphamide group received high-dose melphalan plus salvage ASCT at progression in this study, as retrospective studies have shown an overall survival advantage when salvage ASCT has been used.[14,16,17,21] Long-term follow-up analysis for overall survival will be undertaken in the future, at which point the primary endpoint analysis will also be updated.

Our trial further shows that the quality of responses after salvage ASCT is similar to that after first-line ASCT. We reported a stringent complete response or complete

response in 39% of patients after salvage ASCT, whereas 49% of patients had this response after the first ASCT (appendix). A partial response or very good partial response was reported in 44% of patients after salvage ASCT and in 34% after the first ASCT.

The response to PAD re-induction therapy in this broadly bortezomib-naive population was similar to that seen in front-line trials of PAD therapy.[30] The proportion of patients with an overall response in our trial after four cycles of PAD was 79%, with 17% of patients reaching a complete response or a stringent complete response and 38% achieving a very good partial response or better. In a randomised trial comparing PAD with vincristine, adriamycin, and dexamethasone,[12] 7% of patients had achieved a complete response after three cycles of PAD, with 4% achieving a near-complete response and 42% achieving a very good partial response or better. Depth of response is an important prognostic factor in the front-line transplant setting,[31–33] and the results of our study suggest that the depth of response to re-induction translates into a longer time to progression, but this was not confirmed in our predefined subgroup analysis.

Our trial was designed to incorporate a proteasome inhibitor-based re-induction regimen rather than an immune-modulatory drug (IMiD)-based regimen because of the high level of IMiD exposure in the first-line setting for trial registrants, and also because of access restrictions to treatment with any novel agents across many health-care systems. In many countries worldwide, many patients will relapse from first-line therapy without receiving bortezomib. As such, we used a bortezomib-containing regimen as re-induction therapy to obtain a high extent of tumour control to help to assess which consolidation strategy offered the better balance of efficacy and toxicity. The choice of cyclophosphamide as post-induction consolidation for the control group might be questioned in the current treatment landscape. However, when the trial was designed in 2006, no worldwide standard of care was evident for post re-induction consolidation, although weekly cyclophosphamide was used as a standard of care in the UK in earlier Medical Research Council trials that showed efficacy for cyclophosphamide in the non-transplant setting.[34] Our trial design permitted the comparison of the effect on durability of response by alkylating-agent dose comparison. Time to progression with cyclophosphamide in our study (11 months from randomisation plus a median of 3·8 months from requiring treatment to randomisation) is similar to that of the control group in a study by Garderet and colleagues[26] that received thalidomide and dexamethasone (13·8 months). Furthermore, no maintenance therapy was included as part of the treatments in our trial, because the role of maintenance therapy after salvage ASCT has not been established, even in retrospective studies. Nevertheless, having shown that salvage ASCT has a better durability of response than does cyclophosphamide, and after studies have shown the benefit of consolidation or maintenance strategies in the front-line transplant setting,[6,8,9,12,35] further investigation of therapy after ASCT in the relapse setting is warranted, and we will seek to address this question in a new study. Failure to mobilise stem cells resulted in 30 (11%) of 266 patients not being eligible for randomisation; however, the study design was powered to accommodate a stem-cell mobilisation failure rate of 30%. However, this study had 123 patients who had an adequate amount of stored cells, which suggests that it can be possible to mobilise enough stem cells at first-line ASCT for a second, salvage ASCT, thus making salvage ASCT an option for a third of patients who would be eligible for the procedure, but who might not mobilise a sufficient number of stem cells at relapse. There was no difference in response or outcome for patients who had their salvage ASCT from newly mobilised cells versus stored cells.

As expected, salvage ASCT was associated with more grade 3–4 haematological and gastrointestinal adverse events than was weekly cyclophosphamide. The proportion of patients with grade 3–4 peripheral neuropathy after PAD induction was 12%, which is lower

Panel: Research in context

Systematic review

The management of relapsed multiple myeloma after a previous autologous stem-cell transplant (ASCT) has evolved over the past 10–15 years with the advent of strategies containing new agents. Before this period, and concurrent with such developments, the use of salvage ASCT in the first relapse setting had a role in routine clinical practice. We undertook a systematic review, with no date or language restrictions (PubMed search for "salvage autologous transplant", "second autologous transplant", and "relapsed myeloma"), in 2006 and found seven published studies that were suitable for consideration. A repeat of the systematic review in 2013 found a further 12 studies that were published in the intervening period. Both scientific literature reviews showed that the evidence to support salvage ASCT was based on retrospective registry or single-centre studies only, mainly without the incorporation of new agents in the re-induction phase. The findings of these studies suggested that salvage ASCT provides a benefit in terms of progression-free survival compared with therapy consisting of chemotherapy combinations. Because the published results were limited by their retrospective and non-comparative nature, and were largely done in an era when new anti-myeloma agents were not available, randomised, multicentre data was clearly needed that delineated the true potential for salvage ASCT in relapsed disease, as evidence for clinical decision making and thus practice-changing research.

Interpretation

We show that high-dose melphalan plus salvage ASCT administered at first relapse significantly prolongs time to progression compared with conventional, low-dose alkylating agent (cyclophosphamide) consolidation, after the use of a re-induction regimen containing a new agent. The data provide the necessary prospective evidence not only substantiating the previous retrospective studies in an up-to-date clinical treatment scenario, but also showing the clinical usefulness of salvage ASCT in myeloma at first relapse. Our results might aid the decision-making process for both physicians and patients with myeloma at first relapse.

than that reported in a trial by Sonneveld and colleagues[13] after PAD induction (24%).[13] In our trial, bortezomib was administered intravenously. Moreau and colleagues[36] showed that the subcutaneous administration of bortezomib results in improved tolerability, particularly a reduction in peripheral neuropathy, while retaining the efficacy reported with the intravenous application of the agent,[36] suggesting that the subcutaneous route might be preferable in future studies.

In conclusion, to our knowledge, this trial is the first randomised study to show that salvage ASCT is better than weekly cylcophosphamide in consolidating the response obtained from new-agent re-induction therapy. The clear demonstration of effect on durability of response in the relapse setting provides evidence for salvage ASCT to be considered as a standard of care for eligible patients, although this approach to the clinical management of relapsed myeloma is widely practised in some countries. Although the effect on overall survival remains to be clarified, these results show that salvage ASCT should be routinely considered in eligible patients at first relapse, offering evidence for informed decision making regarding the choice of ASCT for clinicians and patients alike.

Contributors

Authorship was determined in accordance with a pre-determined trial management group policy delineated in the protocol. GC designed the study and GC, JMB, DAC, and TCMM analysed the data. GC wrote the Article and CW, JMB, DAC, JCaven, JAS, AJA, MF, CP, KY, JCavet, HH, JMB, AC, SO'C, MTD, and TCMM obtained the data, revised the Article, and gave final approval.

Declaration of interests

GC and JAS have received honoraria, research funding, and speakers bureau fees from Janssen. CW has received honoraria and speakers bureau fees from Janssen. JC has received research funding from Janssen. All other authors declare no competing interests.

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