Bortezomib consolidation post-ASCT as frontline therapy for multiple myeloma deepens disease response and MRD negative rate whilst maintaining QOL and response to re-treatment at relapse

Oliver C Cohen¹, Nicholas Counsell², Neil Rabin¹, Rakesh Popat¹, Roger G Owen³, Bilyana Popova², Oliver Schofield², Laura Clifton-Hadley² Janet Lyons-Lewis¹, Andy Rawstron⁴, Christopher Spence², Ruth Mary de Tute⁴, Derralynn Hughes⁵, Sally Moore⁶, Paul Smith² and Kwee L Yong⁷

¹Haematology, University College London Hospitals NHS Foundation Trust, London, UK; ²Cancer Research UK and UCL Cancer Trials Centre, London, UK; ³United Leeds Teaching Hospitals, Leeds, UK; ⁴St James Institute of Oncology, HMDS, Leeds, UK; ⁵Department of Haematology, Royal Free Hospital, London, UK; ⁶Royal United Hospitals Bath, Bath, UK; ⁷Cancer Institute, UCL, London, UK

Correspondence: Professor Kwee Yong, UCL Cancer Institute, 72 Huntley St., London, WC1E 6DD.
Email: kwee.yong@ucl.ac.uk
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The current paradigm for treating fit patients with newly diagnosed multiple myeloma (NDMM) is induction chemotherapy followed by consolidation with autologous stem cell transplantation (ASCT) (Gay et al, 2017). Consolidation strategies remain controversial, whereas the benefit of lenalidomide maintenance post-ASCT has been confirmed in several studies (Mikhael, 2017). Bortezomib is a proteasome inhibitor (PI), used both in the front line and relapse setting. Post-ASCT, the incidence of neurotoxicity makes it less attractive for maintenance, but a limited duration of consolidation may be beneficial. The benefits of consolidation with bortezomib monotherapy have been explored using differing protocols with different cumulative doses (Sonneveld et al, 2012, Mellqvist et al, 2013, Einsele et al, 2017).

The study objective was to investigate bortezomib monotherapy for up to 8 cycles in patients receiving upfront ASCT after non-bortezomib containing induction regimens. Primary endpoints were disease response, targeting a 6-month complete response rate of 34%, and treatment tolerability. Secondary endpoints included MRD status at 6 and 12 months after ASCT, progression-free survival from date of registration, quality of life (QoL), outcomes post-salvage regimens, post-relapse and overall survival. The study was approved by the East London and The City Research Ethics Committee (ClinicalTrials.gov identifier: NCT01517724).

Forty patients, enrolled between 2009-2014, received bortezomib (1.3mg/m²) either subcutaneously or intravenously on days 1,8,15 and 22 of a 4-week cycle from 3 months post-ASCT for up to 8 cycles. Disease assessment (IMWG), including MRD (multi-parametric flow cytometry, 10⁻⁴) (Rawstron et al, 2015), was carried out at baseline, and repeated at 6 and 12 months post-ASCT. Patients were monitored annually and details of post-progression therapy recorded. Toxicity and QoL (EORTC-QLQ-C30) were assessed at each cycle. Serum markers of bone formation (basic alkaline phosphatase, bALP and osteocalcin, OC), were measured by ELISA at baseline, 6 and 12 months post ASCT.

Patient characteristics are detailed in Table 1. Of 40 patients, 34 patients were evaluable for disease response (4 received <2 cycles, 1 had non-secretory disease and 1 withdrew consent). Biochemical
responses at trial entry were: 4 (11.8%) sCR/CR, 19 (55.9%) VGPR, 10 (29.4%) PR and 1 (2.9%) SD. At 6 months post-ASCT, 5 patients (14.7%) achieved sCR/CR, 23 (67.6%) VGPR and 6 (17.6%) PR. Disease responses improved further by 12 months post-ASCT, with 7 (20.6%) patients achieving sCR/CR, and 22 (64.7%) VGPR (Supp Figure 1). Nineteen patients had paired MRD assessments at 3/6 and 12 months post-ASCT: 10 were MRD positive at the earlier time point, of whom 4 converted to MRD negativity, whilst 9 patients were MRD negative at both times. Accounting for both modalities, a total of 15 patients (44.1%) had improved their response at 12 months.

With median follow-up of 55.9 months, 12/40 patients (30.0%) are alive without progression, 24 (60.0%) are alive but have progressed, and 4 (10.0%) patients have died following progression. Median PFS from registration was 38.3 months (95% CI: 34.2-42.4) and 41.6 months (95% CI: 37.3-41.6) from ASCT. Patients who were MRD negative at 12 months had a median PFS of 44.0 months (95% CI: 32.3-55.8) compared with 22.0 months (95% CI: 21.5-22.6) for MRD positive patients (HR=3.61, 95% CI: 1.33-9.79; p=0.01) (Figure 1). Median PFS was 44.0 months (95% CI 35.2-52.8) for patients who were MRD negative at both time points (N=9), 23.4 months (95% CI: 16.4-30.3) for patients who converted from MRD positive to MRD negative (N=4), and 21.8 months (95% CI: 17.0-26.6) for patients who remained MRD positive at both time points (N=6). We show, for the first time, that single agent bortezomib as consolidation post-ASCT improves MRD negativity rate, which should in turn lead to longer PFS in these MRD negative patients.

Of the 39 patients who received any drug, 15 (38.5%) had a dose modification, 22 (56.4%) had a dose delay and 28 (71.8%) had a dose omitted. There were 18 grade ≥3 AEs in 13 patients (Supp Table 1). Incidence of sensory neuropathy was lower in patients receiving SC compared to IV bortezomib (Supp Table 2). Four serious adverse events occurred; 3 non-neutropenic infections, 1 supraventricular tachycardia. EORTC-QLQ-C30 scores did not change significantly throughout the study (Supp Figure 2). Osteoblast markers were higher in patients with a deeper response (CR/VGPR) when compared to those in PR or less (p=0.04 and 0.03 for bALP and OC respectively) (Supp Figure 3) but neither marker changed significantly following bortezomib consolidation.

Of the 28 patients who have progressed, 13 (46.4%) received bortezomib-based salvage regimens, 5 (17.9%) received carfilzomib-based regimens and 10 (35.7%) have not started second-line therapy. Overall response with bortezomib salvage was 76.9% (6 VGPR, 4 PR and 3 SD). Four patients proceeded to a second ASCT. In the 18 patients receiving salvage, median 2nd PFS from start of second line was 17.7 months (95% CI: 13.7-21.7). Median PFS2 from registration was 71.4 months (95% CI: 54.1-88.8). This suggests that prior bortezomib use does not compromise efficacy as salvage therapy. While next generation PIs and monoclonal antibodies are emerging on the scene both in first line treatment and at relapse, the re-use of bortezomib at relapse is likely to continue especially in countries with limited access to newer agents.

In summary, weekly bortezomib as consolidation following ASCT is well tolerated and can deepen both biochemical and MRD-defined response depth. Disease-free survival compares favorably to published consolidation protocols using bortezomib (Einsele et al, 2017; Mellqvist et al, 2013); the longer PFS in our study may relate to the higher target cumulative dose of bortezomib (44.8mg/m², cf 26mg/m² and 25.6mg/m² in the Nordic, and German studies respectively). The benefit of higher cumulative dose achieved with weekly scheduling has also been noted in the non-ASCT setting (Mateos et al, 2014). While multi-agent consolidation regimens may be warranted in patients with
high risk disease (Nooka et al., 2014), single agent PI regimens that are well tolerated and affordable are attractive, particularly for non-adverse risk patients.

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KY was responsible for study concept.

KY, NR and RO designed the study.

OC, KY and NC analysed data and wrote the letter.

RP, BP, OS, SM, JL, AR, CS, LC, RD, DH and PS carried out the study.

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References


