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1982 Myeloma Canada Research Network (MCRN)-001 Trial Utilizing Bortezomib (btz)-Based Induction, Enhanced Conditioning with IV Busulfan + Melphalan (BuMel) and Lenalidomide (len) Maintenance in Multiple Myeloma Patients Eligible for Autologous Stem Cell Transplant (ASCT): A National Canadian Study Evaluating Achievement of Minimal Residual Disease (MRD) Negativity and Involved Serum Hevylite™ chain (HLC) Normalization

Clinical Autologous Transplantation: Results
Program: Oral and Poster Abstracts
Session: 731. Clinical Autologous Transplantation: Results: Poster I

Saturday, December 5, 2015, 5:30 PM-7:30 PM
Hall A, Level 2 (Orange County Convention Center)

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As therapy for MM improves, methods more sensitive than conventional serum/urine electrophoresis/immunofixation are required to optimally evaluate response. Our phase 2 multi-center clinical trial, conducted in 10 Canadian centers, utilized serial bone marrow aspirate (BMA) samples for MRD analysis by 8-color multiparameter flow cytometry (MFC), along with serum Hevylite assay of the involved heavy light chains (HLC), to assess responses after ASCT and during maintenance therapy.

After btz-based induction therapy (usually CyBorD), pts without progression received enhanced conditioning with BuMel (IV busulfan 3.2 mg/kg days -5 to -3 or days -6 to -4 + melphalan 140 mg/m^2 day -2 or day -3) followed by ASCT on day 0. On day 100 post-ASCT, lenalidomide (len) 10 mg/day was commenced, escalated to 15 mg/day after 3 cycles if appropriate, and continued until progression. BMA and serum samples were shipped centrally for MRD and Hevylite analysis before induction therapy, before ASCT, on day 100 post-ASCT, every 3 mos for the

MRD and Hevylite analysis before induction therapy, before ASCT, on day 100 post-ASCT, every 3 mos for the 1st year and every 6 mos until progression.

From 03/2013 - 07/2015, 122 newly diagnosed pts provided BMA samples for MRD analysis. To date, 70 pts (target 78), have completed induction therapy and undergone ASCT; 8 others provided pre-induction samples and are expected to be enrolled. 44 of the 122 (36%) who provided BMA samples did not proceed to BuMel due to: poor samples-4 pts (3.2%); MM not confirmed-3 pts (2.5%); prior therapy-1 pt (0.8%); death during induction-1 pt (0.8%); consent withdrawal/opted for standard conditioning-19 pts (15.6%); and no ASCT-16 pts (13.1%; 8 were unfit, 4 had comorbidities, 2 progressed, 1 failed mobilization and 1 received tandem ASCT for high-risk MM). Median follow-up is 17.4 mos (range: 6.3-25.6).

Median age is 57 (34-69); 64% are male. Median serum β2-microglobulin level is 3.07 mg/L (1.5-20) and albumin 37 g/L (2.8-48.1); 31 pts have ISS stage I; 18 stage II; 15 stage III MM and 6 have missing data. Ig subtype includes IgGκ in 30 (43%), IgGλ in 14 (20%), IgAκ in 8 (12%), IgAλ in 9 (13%), κ in 5 (7%); λ in 1 (1%) and missing data in 3 pts (4%).

Post-ASCT, 14 SAEs have occurred: Grade 3 atrial fibrillation (2), acute kidney injury (3), increased creatinine (1), upper respiratory infection (2), febrile neutropenia (2), bacteremia (1), hypoxia (1) and lung infection (1) and Grade 4 sepsis (1). There have been no ASCT-related deaths; 4 pts have progressed.

The best conventional Ig response post-induction in the 66 pts with available data is CR in 5 (7.6%), VGPR in 25 (38%), PR in 31 (47%), MR in 4 (6%) and SD in 1 (1.5%). The Ig response at day 100 in the 60 evaluable pts includes CR in 10 (17%), VGPR in 30 (50%), PR in 18 (30%), MR in 1 (1.5%) and SD in 1 (1.5%). MRD negativity improved from 18/67 (27%) after induction to 22/60 (37%) at day 100 (Table 1). Among evaluable pts, 83.3% of those after induction and 68.2% of those at day 100 who were MRD-negative had normal involved HLC ratios, while 42.6% and 51.5% of those who were MRD-positive, respectively, had normal ratios.

Table 1. Response Rates by Conventional Serum/Urine Parameters and Marrow Flow Cytometry for MRD

				MRD Negativity by Conventional Ig Respor								
	# Evaluable	Normal Hevylite ratio (# normal /evaluable) (%)	# MRD Negative (%)	CR		VGPR		PR		MR		SD
				Total	MRD(-)	Total	MRD(-)	Total	MRD(-)	Total	MRD(-)	Total	MI
After Induction	67	15/18 (83.3%)	18 (27%)	5	4	25	9	31	5	4	0	1	
Day 100 Post-ASCT	60	15/22 (68.2%)	22 (37%)	10	4	30	16	18	2	1	0	1	

Conclusions: 1) IV BuMel conditioning + ASCT was well-tolerated with few SAEs and no ASCT-related deaths; 2) at day 100 post-ASCT, 97% had achieved ≥ PR (≥ VGPR in 67% and CR in 17%); 3) MRD negativity rates improved from 27% to 37% after ASCT; 3) conventional Ig and MRD responses were often discordant as only 40% of CR pts were MRD-negative at day 100; 4) the majority of MRD-negative patients also had normalization of their involved HLC ratios; 5) further F/U is required to determine the rate of achievement of MRD negativity during maintenance therapy; relationships between conventional Ig response, MRD status and involved HLC ratio; and

maintenance therapy), relationships between conventional Ig response, MRD status and revised ISS ratio, and long-term outcomes with this approach.

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