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Myeloma Canada Research Network (MCRN)–001 ASCT Study of Busulfan + Melphalan (BuMel) Conditioning Followed By Lenalidomide (Len) Maintenance: Updated Results Including Serial Minimal Residual Disease (MRD) and Involved Serum Hevylite™ Chain (HLC) Ratio Assessments

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Abstract

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MRD negativity has become an important goal of the initial treatment of MM pts. Our phase 2 multi-center clinical trial, conducted in 10 major Canadian transplant centers, was designed to increase the MRD negativity rate after ASCT by using conditioning with 2 high-dose alkylating agents followed by len maintenance. In addition to conventional response criteria, this trial evaluated serial bone marrow aspirate (BMA) samples for MRD analysis by 8-color multiparameter flow cytometry (MFC) along with serum Hevylite™ assays of the involved HLC that were obtained before and after ASCT and during maintenance therapy.

After bortezomib (btz)-based induction therapy off study, pts without MM progression received BuMel (busulfan 3.2 mg/kg IV days -5 to -3 or days -6 to -4 + melphalan 140 mg/m^2 day -2 or day -3) conditioning, followed by ASCT on day 0. On day 100 post-ASCT, len 10 mg/day was started, escalated after 3 cycles to 15 mg/day 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 1st year and every 6 mos until progression.

Between 03/2013 - 05/2016, 125 newly diagnosed pts provided BMA samples for MRD analysis. To date, 76 pts (target 78), have completed induction therapy and undergone ASCT; 2 pts have provided initial samples and are expected to be enrolled. 46 of the 125 (36.8%) who provided BMA samples did not proceed to BuMel due to: poor samples - 4 (3.2%); MM not confirmed - 3 (2.4%); prior therapy - 1 (0.8%); death during induction - 1 (0.8%); consent withdrawal/opted for standard conditioning - 21 (16.8%); and no ASCT - 16 (12.8%) (8 were unfit, 4 had comorbidities, 2 progressed, 1 failed mobilization and 1 underwent preferential tandem ASCT). Median follow-up is 27.4 mos (range: 10.4-37.6).

Median age is 57 (34-69); 65.8% are male. Median serum β2-microglobulin level is 3.07 mg/L (1.5-20) and albumin 37 g/L (2.8-48.1); 34 pts have ISS stage I; 21 stage II; 17 stage III MM and 5 have missing data. Ig isotype includes IgGκ in 34 (44.7%), IgGλ in 16 (21.1%), IgAλ in 10 (13.2%), IgAκ in 9 (11.8%) and κ in 7 (9.2%).

Post-ASCT, 26 SAEs have occurred: Grade 2: atrial fibrillation (1) and URI (1); Grade 3: atrial fibrillation (1), acute kidney injury (4), infectious enterocolitis (2), gallbladder infection (1), URI (1), febrile neutropenia (3), bacteremia (1), pain in extremity (1), hypoxia (1), pleural effusion (1), and 3 lung infection (4); and Grade 4: sepsis (1), AML [with spontaneous regression] (1), respirato distress (1) and acute kidney injury (1). There have been no ASCT-related deaths; 11(14.4%) pts have progressed.

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The best conventional Ig response post-induction in the 76 evaluable pts is CR in 6 (7.9%), VGPR in 29 (38.2%), PR in 35 (46.1%), MR in 5 (6.6%) and SD in 1 (1.3%). At day 100 after ASCT, the Ig response in the 73 evaluable pts is CR in 9 (12.3%), VGPR in 41 (56.2%), PR in 22 (30.1%) and MR in 1 (1.4%). The rates of MRD negativity also increased from 29% after btz-based induction to 41%, while the rates of achievement of a normal HLC ratio were 50% after induction and 48% at day 100 (Table 1). Among evaluable pts, 77.3% of those after induction and 53.3% of those at day 100 who were MRD-negative also had had normal involved HLC ratios, while 38.9% and 44.2% of those, who were MRD-positive, respectively, had had normal involved HLC ratios. At month 6 and 12 post-ASCT, 43% and 35% of evaluable pts, respectively, are MRD-negative. Individual patient patterns of len dose, MRD negativity and involved HLC ratios are under assessment and will be presented.

Conclusions: 1) IV BuMel conditioning + ASCT is well-tolerated with few SAEs and no ASCT-related deaths; 2) at day 100 post-ASCT, 98.6% had achieved ≥ PR (≥ VGPR in 68.5% and CR in 12.3%); 3) MRD negativity rates improved from 29% to 41% after ASCT; 4) the rates of normalization of the involved HLC ratio remained stable (50% to 48%) pre- and post-ASCT; 4) conventional Ig and MRD responses were often discordant as only 41% of CR pts were MRD-negative at day 100; 5) the majority of MRD-negative patients (53.3%) also had normalization of their involved HLC ratios; 5) with a median follow-up of over 2 years, only 14% of pts have progressed; 6) the serial marrow samples mandated by this study will allow determination of relationships between len dose, conventional Ig response rates, MRD status and involved HLC ratios as these pts are followed for longer periods of time.

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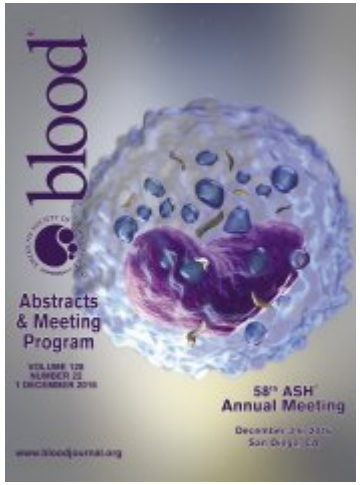

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