First Report of the Myeloma Canada Research Network (MCRN)-001 Trial Utilizing Bortezomib-Based Induction, Enhanced Conditioning with IV Busulfan + Melphalan (BuMel) and Lenalidomide Maintenance: Feasibility of a National Canadian Study Based on Achievement of Minimal Residual Disease (MRD) Negativity

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Blood 2014 124:3990;

Abstract
Conventional immunoglobulin (Ig) markers have been used to define multiple myeloma (MM) responses, but assessment of marrow for minimal residual disease (MRD) may provide better information on disease status/prognosis (Paiva B, et al. Blood 2008; 112: 4017). We therefore initiated a national multi-center ASCT trial with the goal of producing a high rate of MRD-negativity by using bortezomib (btz)-based induction, enhancing the conditioning regimen and utilizing post-ASCT maintenance.

This phase 2 open label-trial was conducted in 10 Canadian centers. After btz-based induction (usually CyBorD) in the absence of disease progression, patients (pts) received BuMel conditioning (IV busulfan 3.2 mg/kg days -5 to -3 or days -6 to -4 + melphalan 140 mg/m² 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 disease progression.

Bone marrow aspirate (BMA) samples were shipped centrally for MRD analysis by 15-color multiparameter flow cytometry (MFC) before any therapy, prior to ASCT, on day 100 post-ASCT, every 3 mos for the 1st year and every 6 mos thereafter until progression.

Between 03/2013 – 07/2014, 99 newly diagnosed MM pts provided untreated BMA samples for MRD analysis. To date, 42 of a planned target of 78 pts have completed induction therapy have undergone ASCT and 39 are evaluable so far. 25 of the 99 (25%) who provided initial marrow samples did not meet criteria for enrollment: 3 (3%) had poor BMA samples; 3 (3%) did not have confirmed MM; 6 (6%) did not proceed with ASCT (1 due to progression); 1 (1%) had received dexamethasone prior to MRD analysis; 1 (1%) died during induction and 11 (11%) withdrew consent/opted for standard conditioning.

Median age of the 39 evaluable pts is 53 (39–67); 64% are male. Median serum β2-microglobulin level is 3.64 mg/L (1.7–20); albumin 37 g/L (2.8–48.1); 17 pts have ISS stage I; 9 have stage II; 9 have stage III MM and 4 have missing data. Ig subtype includes IgGκ in 16 (40%), IgGλ in 4 (10%), IgAκ in 5 (13%), IgAλ in 8 (21%), IgMλ in 1 (3%), κ in 1 (3%); non-secretory in 2 (5%) and no data in 2 pts (5%).

Post-ASCT, only 4 SAEs have occurred: atrial fibrillation (2), acute kidney injury (1) and sepsis (1). There have been no ASCT related deaths, and no pt has progressed at a median follow-up of 7.8 mos (range: 4.8–10.1).

The best Ig response post-induction in the 31 pts with available restaging data is CR in 5 (16%), VGPR in 9 (29%), PR in 13 and SD in 1 (3%). 27 pts have reached day 100 post-ASCT and 8 pts have been formally evaluated. In these 8, the Ig response is CR...
in 2 (25%), VGPR in 5 (63%) and PR in 1 (12%). Table 1 summarizes MRD results to date.

<table>
<thead>
<tr>
<th>Time point of assessment</th>
<th># Evaluable</th>
<th>Total # MRD negative</th>
<th>CR</th>
<th>VGPR</th>
<th>PR</th>
<th>MR</th>
</tr>
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<tbody>
<tr>
<td>Day 100 post-ASCT</td>
<td>8</td>
<td>2</td>
<td>2 [2]</td>
<td>5 [0]</td>
<td>1 [0]</td>
<td>0</td>
</tr>
<tr>
<td>During lenalidomide maintenance</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>5 [1]</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 1. Comparison of conventional Ig response rates and achievement of MRD negativity

Conclusions: 1) MFC performed on pre-therapy marrow samples to allow subsequent evaluation for MRD was successful in 97% of pts using a central lab; 2) IV BuMel was well-tolerated with few SAEs and no ASCT-related deaths; 3) MRD and conventional Ig responses may not correlate well; 4) Further F/U is required to determine the dynamics of MRD achievement and long term outcomes with this approach.

Potential Articles of Interest

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
Jean Roy et al., Blood

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 HevyliteTMÂ chain (HLC) Normalization
Jean Roy et al., Blood

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
Jean Roy et al., Blood

Ixazomib-Lenalidomide-Dexamethasone (IRd) Combination before and after Autologous Stem Cell Transplantation (ASCT) Followed By Ixazomib Maintenance in Patients with Newly Diagnosed Multiple Myeloma

VRD Plus Lenalidomide Maintenance Yields Good Results in De Novo Myeloma
PracticeUpdate

Evidence Mounts for Early Treatment of Smoldering Myeloma
PracticeUpdate

HIV-1–Associated Atherosclerosis
PracticeUpdate

After ASCT in Multiple Myeloma, Bortezomib/Lenalidomide Consolidation Leads to Improved Survival Without Skeletal-Related Events
Evangelos Terpos, PracticeUpdate(US)

Oral Ixazomib Maintenance Following Auto-SCT
Prof Meletios A Dimopoulos, MD, PracticeUpdate(US)
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