Panthera R&D Program for Hemato-Oncology

Ultra High-Risk Multiple Myeloma Patients with Multi-Hit Tumours and SKY92 High Risk Signature Are at Increased Risk of Early Relapse Even When Treated with Extended Intensified Induction and Consolidation - Results from the Optimum/Muknine Trial

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Introduction

We recently reported improved outcomes for patients with ultra-high risk (UHiR) newly diagnosed multiple myeloma (NDMM) by double hit/≥2 high-risk cytogenetic abnormalities (HRCA) and/or SKY92 risk signature or primary plasma cell leukemia (pPCL) in the OPTIMUM/MUKnine (NCT03188172; Kaiser et al, JCO 2023) trial. However, some participants still relapsed within the first 18 months of treatment despite stratified intensive therapy with Dara-CVRd, V-ASCT and extended Dara-VR(d) consolidation. In this analysis we characterise factors associated with early progression.

Methods

In OPTIMUM, patients with UHiR NDMM (≥2 HRCA: t(4;14), t(14;16), t(14;20), gain(1q), del(1p), del(17p) or SKY92 high risk signature) or with pPCL received up to 6 cycles of Dara-CVRd induction, V-ASCT, 6 cycles Dara-VRd (Cons1) and 12 cycles Dara-VR (Cons2), before moving to monthly Dara-R maintenance until progression. OPTIMUM recruited 107 UHiR patients, including 9 pPCL. In this exploratory analysis, baseline clinical, laboratory and tumour molecular characteristics were compared between patients who experienced an Early Relapse, defined by MM relapse or MMrelated death within 18 months from registration and those who did not, using descriptive statistics and hypothesis testing using two-sample t-tests or chi squared tests. Baseline characteristics were also compared by minimal residual disease (MRD; 10 sensitivity by flow cytometry) status at the end of induction to elucidate whether baseline factors associated with early MRD negativity were overlapping with those associated with Early Relapse. Median follow-up was 51.5 months, and all patients had been on study for over 44 months

Results

Twenty-three (21%) of 107 UHiR patients experienced Early Relapse, versus 84 (79%) who did not. Patient age and gender were not different between groups. Platelet levels as a continuous variable were lower in the Early Relapse group vs those without (mean 179/nL, standard deviation (SD) 92/nL vs. mean 223/nL, SD 77/nL; P=0.0247), whereas haemoglobin, serum creatinine, calcium, presence of soft tissue plasmacytomas (PCM), bone lytic lesions or plasma cell bone marrow infiltration on diagnostic trephine were similar.

ISS stage distribution differed between groups (P=0.0203): most Early Relapse participants were ISS stage 2 (13/23 (56.5%) vs 30/84 (35.7%) without Early Relapse), whereas ISS stage 3 was nominally similar (34.8% vs 31.0%). Most notably, only one of the 29 ISS stage 1 patients in OPTIMUM experienced Early Relapse. 57 of 107 (53.3%) patients entered OPTIMUM with ≥2 HRCA at diagnosis, and, of these, seven carried 3 HRCA. Five of seven participants (71.4%) with 3 HRCA experienced Early Relapse,

opposed to only seven out of 50 (14%) with only 2 HRCA. 82 of 107 (76.6%) were SKY92 high risk at baseline. Only two of the 24 participants (8.3%) with SKY92 standard risk experienced Early Relapse, as opposed to 20 out of 82 (24.4%) with SKY92 high risk. Of individual HRCAs, only presence of del(17p) was associated with early relapse (P=0.002): 8 of 16 (50%) participants with del(17p) tumours experienced Early Relapse. However, seven of these 8 Early Relapse del(17p) tumours (88%) were also positive for SKY92 high risk signature. In contrast, the majority (62%) of del(17p) that did not relapse early were SKY92 standard risk. Of the 107 UHiR patients, 6 did not reach end of induction and 14 had no MRD result. Of 87 participants with interpretable MRD result at end of induction (EOI), 51% tested MRD-negative (44/87). Of clinical factors, only presence of PCM was associated with insufficient response (P=0.017, 5/5 MRD-positive), whereas ISS stage was not associated with MRD at EOI. Only one of four participants (25%) with 3 HRCA had MRD-negative status at EOI vs 66% of those with 2 HRCA. Also, the majority of patients (62%) identified by SKY92 high risk only were still MRD-positive.

Conclusions:

Our results suggest that presence of 3 or more HRCA, SKY92 high risk signature or del(17p) combined with SKY92 high risk are all associated with increased risk of Early Relapse despite intensified OPTIMUM treatment, and could help identify patients early who are candidates for novel, innovative first-line therapeutic approaches. Results also suggest utility of integrated molecular diagnostics, including gene expression risk profiling, to support clinical decision making in the era of advanced front-line combination therapies.

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