4. SPECIAL CONDITIONS

FUNCTIONAL HIGH RISK MULTIPLE MYELOMA IN THE ANTI-CD38 QUADRUPLET ERA: REDEFINITION THROUGH REAL WORLD DATA

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Introduction. Functional high-risk (FHR) multiple myeloma (MM) is currently defined as relapse within 12 or 18 months (mo) from the start of conventional therapy or induction followed by autologous stem cell transplantation (ASCT), irrespective of baseline risk. The introduction upfront of quadruplet regimens (QUAD) incorporating anti-CD38 monoclonal antibodies (mAb) has led to a substantial outcome benefit, particularly in ASCT eligible (TE) patients. Consequently, an update of the current FHR definition is warranted to reflect outcomes achieved with modern QUAD-based approaches. Recently, Costa et al. proposed 36 mo as a new FHR threshold, based on TE MM patients treated with QUAD plus ASCT in the MASTER trial and an institutional cohort.

Methods. We conducted a retrospective analysis of TE patients with newly diagnosed MM (NDMM) treated at 12 Italian centers, who were stratified into two groups according to frontline therapy: anti-CD38–based QUAD and triplet regimens without anti-CD38 mAb (TRIPL). Different FHR definitions were assessed by applying distinct progression cutoffs at 12 (FHR12), 18 (FHR18), 24 (FHR24), and 36 months (FHR36) from treatment initiation. Univariate and multivariate Cox regression analysis was performed to assess the best cut-off of PFS and the other factors affecting Overall Survival (OS).

Results. The study comprised 404 transplant eligible NDMM patients, of whom 186 received QUAD therapy and 218 TRIPL therapy. QUAD regimens included Dara VTD (162), Dara VCD (12), Dara VRD (10), and Isa KRD (2) whereas TRIPL therapy VTD (203), CyBorD (8) and VRD (7). Baseline characteristics were comparable between the two groups. Among patients receiving QUAD therapy, 28% were older than 65 years, compared with 20% in the TRIPL group. An ECOG performance status ≥2 was reported in 13% and 10% of patients, respectively. ISS stage III was observed in 22% of QUAD and 21% of TRIPL patients, while R ISS stage II–III accounted for 60% and 65%, respectively. High risk cytogenetic abnormalities were present in 26% of QUAD and 30% of TRIPL patients. A platelet count <150,000/mm^3 was documented in 16% of QUAD and 19% of TRIPL patients. A response ≥VGPR was achieved by 89% and 84.5% of patients receiving QUAD and TRIPL regimens, respectively. After a median follow-up of 40.2 mo, PFS was significantly longer in the QUAD compared to TRIPL group (NR vs 61 mo; p= 0.038). The cumulative incidence of progression among QUAD-treated vs TRIPL-treated patients was 3% and 3.6% for FHR12, 5.3% and 7.5% for FHR18, 9.8% and 9.8% for FHR24, 16.3% and 24.5% for FHR36 (p=0.035). In the multivariate analysis, progression within 36 months from treatment initiation (vs >36 months) was independently associated with inferior OS (HR 4.1, 95% CI 1.6–6.3, p=0.004), together with FISH high risk cytogenetics (HR 2.3, 95% CI 1.2–4.9, p=0.028). Conversely, receipt of QUAD therapy was associated with improved OS (HR 0.6, 95% CI 0.2–0.8, p=0.005).

Conclusions. While early progression rates at 12 and 24 months were comparable between treatment groups, a clear separation emerged at 36 months, with a substantially lower cumulative incidence of progression in patients treated with QUAD. In the context of anti-CD38–based QUAD followed by ASCT, FHR MM should be redefined as disease progression occurring within the first 36 months of therapy, providing a more accurate and clinically meaningful framework for risk stratification and future trial design.