2. NEWLY DIAGNOSED MULTIPLE MYELOMA

WHEN TRIAL DESIGN MEETS APPROVED MAINTENANCE: A SINGLE-CENTER REAL-WORLD EXPERIENCE WITH DARA-VTD INDUCTION AND CONSOLIDATION FOLLOWED BY LENALIDOMIDE MAINTENANCE IN TRANSPLANT-ELIGIBLE MULTIPLE MYELOMA

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Introduction. Based on the CASSIOPEIA trial, Dara-VTd represents the frontline induction regimen for transplant-eligible multiple myeloma (MM) in Italy, followed by ASCT and Dara-VTd consolidation. While daratumumab maintenance showed clinical benefit, it is not approved in this setting; therefore, lenalidomide maintenance has been adopted after Dara-VTd. This has generated a widely used real-world treatment sequence for which prospective outcome data are lacking. We report our single-center experience with Dara-VTd followed by lenalidomide maintenance since the Italian approval of Dara-VTd.

Patients and Methods. We retrospectively analyzed 103 newly diagnosed transplant-eligible MM patients (median age 61 years) treated between January 2022 and December 2024 with Dara-VTd induction, followed by ASCT, Dara-VTd consolidation, and lenalidomide maintenance, using an intention-to-treat approach. MRD was assessed by 8-color flow cytometry (sensitivity 10^{-5}) before maintenance and after one year, when available. Response rates, progression-free survival (PFS), and overall survival (OS) were analyzed.

Results. Among 103 patients, 19 (18%) had ISS stage III disease and 15 (15%) had high-risk cytogenetics (IMS-IMWG 2025 definition). Twenty-four patients (23%) underwent double ASCT with MEL200 conditioning. Sixteen patients (15%) were refractory to induction or relapsed early after ASCT, while two did not undergo ASCT due to PBSC collection failure. Post-consolidation responses were PR 8%, VGPR 20%, CR 52%, and sCR 9%. MRD negativity before maintenance was observed in 69 patients (67%); 9 patients were MRD-positive (9%, including 2 with high-risk cytogenetics), while 25 were not assessed due to early progression or missing samples. At data cut-off, 83% of patients had started lenalidomide maintenance. After a median follow-up of 32 months, 2-year PFS and OS were 83% and 91%, respectively. One-year MRD assessment was available in 25 patients: 21 were MRD-negative and 4 MRD-positive, with three conversions during maintenance: one MRD-negative to positive and two MRD-positive to negative. Two-year PFS was significantly longer in MRD-negative versus MRD-positive patients (98% vs 67%; $p < 0.0001$; HR 0.09, 95% CI 0.01–0.99), as was 2-year OS (100% vs 67%; $p = 0.0025$; HR 0.12, 95% CI 0.01–1.6). Patients with high-risk cytogenetics had inferior outcomes compared with standard-risk patients (2-year PFS 64% vs 87%, $p = 0.0028$; HR 0.26, 95% CI 0.06–1.12; 2-year OS 73% vs 95%, $p < 0.0001$; HR 0.15, 95% CI 0.03–0.83).

Conclusion. In this intention-to-treat real-world experience, outcomes were excellent in standard-risk patients treated with Dara-VTd followed by lenalidomide maintenance. In contrast, patients with high-risk cytogenetics according to the IMS-IMWG 2025 classification showed inferior outcomes as well as those with MRD-positivity after consolidation. These findings suggest that single-agent lenalidomide maintenance may be suboptimal in MRD-positive and high-risk patients, who may benefit from intensified maintenance strategies, including doublet regimens or novel immunotherapy-based approaches. The proportion of refractory or suboptimal responding patients further supports the need for alternative frontline strategies for high-risk MM, as emerging from dedicated clinical trials.