3. RELAPSED/REFRACTORY MULTIPLE MYELOMA

CIRCULATING PLASMA CELLS AS A DYNAMIC BIOMARKER IN MULTIPLE MYELOMA PATIENTS RECEIVING CAR-T AND BISPECIFIC ANTIBODY THERAPY

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Chimeric antigen receptor T-cell (CAR-T) therapy and bispecific antibodies (bsAbs) have profoundly reshaped the treatment landscape of relapsed/refractory multiple myeloma (R-RMM). Despite their efficacy, standardized tools for early response assessment and peripheral residual disease (PRD) monitoring remain limited. Circulating plasma cells (CPCs), including monoclonal (mCPCs) and polyclonal (pCPCs) populations, represent a minimally invasive biomarker reflecting disease activity and dissemination. A total of 55 RRMM patients were included in the study: 21 treated with CAR-T cells and 34 with bsAbs. Patients had a median age of 64 years and had received a median of four prior treatment lines. Longitudinal monitoring was performed using high-sensitivity multiparametric flow cytometry (limit of detection $\geq 10^{-5}$) on 266 peripheral blood samples collected according to a standardized timeline: pre-infusion, day 0, day +7, month 1, and every three months thereafter. In particular, if CPCs were absent before infusion, evaluations were continued at each scheduled time point to detect their emergence, whereas if CPCs were present before infusion, patients were monitored monthly until complete clearance, after which the standard monitoring schedule was resumed. Overall, CPCs were detected at relapse prior to infusion in 32/55 patients (58%), while 23 (42%) had no detectable CPCs. Among CPC-positive patients, 25 (78%) harbored mCPCs and 7 (22%) pCPCs. Median CPC frequency was higher in mCPCs compared with pCPCs (0.0225% vs 0.0067%). In bsAbs-treated patients, CPCs were detected in 59% of cases before infusion, with higher median levels in mCPCs compared with both newly diagnosed MM and CAR-T–treated patients. In the CAR-T cohort, CPCs were identified in 62% of patients, predominantly monoclonal, and displayed an aberrant immunophenotype characterized by high CD138 expression and loss of adhesion and maturation markers, consistent with marrow escape and clonal evolution. No major differences in CPCs prevalence were observed between CAR-T and bsAbs therapies, indicating that circulating disease represents a shared biological feature in RRMM. Early CPCs clearance emerged as a key clinical parameter. Among evaluable CPCs-positive patients, 48% achieved complete CPCs clearance by day +7. All patients presenting with pCPCs cleared CPCs by day +7, whereas persistence was exclusively observed in mCPCs. Patients with early CPCs clearance showed higher rates of complete response (≥CR) compared with those with persistent CPCs. At one month and three months, the majority of patients with early clearance, maintained PRD negativity, whereas CPCs persistence or reappearance was associated with stable or progressive disease. Importantly, day +7 proved to be a robust early time point to discriminate responders from non-responders. In conclusion, CPCs are frequently detectable in RRMM patients undergoing CAR-T or bsAbs therapy, with monoclonal CPCs representing the dominant and clinically relevant circulating population. Early CPCs clearance, particularly by day +7, strongly correlates with sustained PRD negativity and treatment response, supporting the use of standardized CPCs monitoring as an early, non-invasive biomarker to guide response assessment and therapeutic decision-making in immunotherapy-treated MM. *Acknowledgments: RC2025-2797269.*