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(S192) IMPACT OF T-CELL CHARACTERISTICS ON RESPONSE AND RESISTANCE TO T-CELL REDIRECTING BISPECIFIC ANTIBODIES IN MULTIPLE MYELOMA

Topic: 13. Myeloma and other monoclonal gammopathies - Biology & translational research

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Background:

Bispecific antibodies (BsAbs) directed against B-cell maturation antigen (BCMA; teclistamab) or the orphan G protein-coupled receptor GPRC5D (talquetamab) induce deep and durable responses in heavily pretreated multiple myeloma (MM) patients. We have previously shown that high baseline regulatory T-cell (Treg) counts and low T-cell to MM cell (effector to target)-ratio are associated with poor activity of both BCMA- and GPRC5D-targeting BsAbs. However, mechanisms underlying primary and acquired resistance remain poorly understood.

Aims:

The aim of this study was to evaluate the phenotype and functional characteristics of T-cells in serial peripheral blood (PB) and bone marrow (BM) samples from MM patients before and during BsAb therapy.

Methods:

T-cell phenotype was assessed by flow cytometry in serial BM samples obtained from MM patients who were treated with teclistamab or talquetamab (at baseline, after 2 and ±10 months of treatment, and at the time of progression). To assess the cytotoxic potential of these T-cells, we tested these T-cells against the MM cell line RPMI-8226 in *ex vivo* cell kill assays in the presence of solvent control, teclistamab or talquetamab. T-cell proliferation was evaluated by co-culturing violet tracer-labeled PB-mononuclear cells with CD3/CD28-coated beads, or with RPMI-8226 cells in the presence of solvent control, teclistamab or talquetamab.

Results:

Comprehensive phenotyping of BM samples derived from 25 patients treated with teclistamab or talquetamab, showed that responding patients (≥PR; n=17) had lower proportions of PD-1+ CD4+ T-cells (median: 12.9 vs 25.2%, P=0.02), CTLA4+ CD4+ T-cells (median: 1.1 vs 3.7%, P=0.01), and CD38+ CD4+ T-cells (median: 5.6 vs 15.5%, P=0.04) at baseline, compared to non-responders (n=8). Tregs of non-responding patients were more frequently CD38+ compared to those from responders (10.9 vs 4.8%; P=0.04). Although this lack of response was linked to an increase in expression of inhibitory receptors, increasing T-cell/MM cell-ratios by adding extra autologous T-cells, or healthy-donor-derived T-cells, to BM samples from poor responders enhanced sensitivity to BsAbs in *ex vivo* experiments.

To investigate the impact of BsAb-mediated T-cell activation on T-cell phenotype, RPMI-8226 tumor cells were co-cultured with T-cells in the presence of teclistamab or talquetamab. After 2 and 4 days of treatment, there was a substantial increase in both activation and exhaustion markers. Similar T-cell phenotypic changes occurred in patients receiving BsAb treatment, with an increased proportion of T-cells expressing exhaustion markers (PD-1, TIGIT, and TIM-3) during treatment, compared to baseline. This was accompanied by reduced T-cell fitness, as evidenced by decreased proliferative potential (panel A for CD3/CD28-coated beads), impaired anti-tumor activity (panel B), as well as diminished granzyme B release

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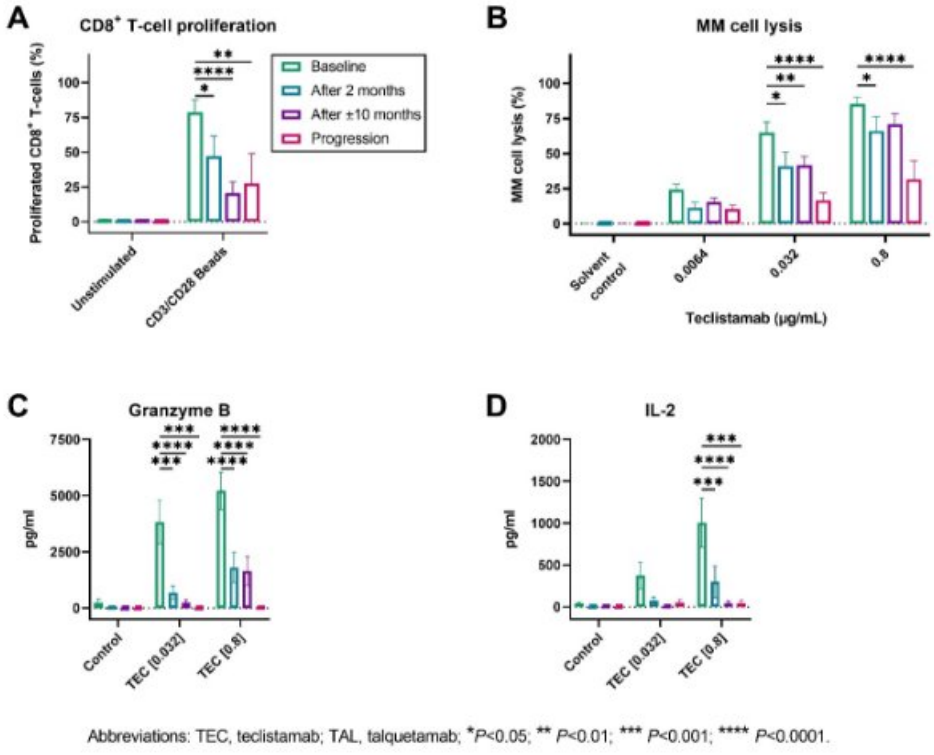
(panel C) and cytokine secretion (panel D for IL-2) in ex vivo experiments. These T-cell phenotypic and functional changes were most pronounced at the time of progression (e.g. mean teclistamab-mediated MM cell lysis [0.8 µg/mL], baseline vs progression: 85.4% vs 31.5%, *P*<0.0001; mean CD3/CD28-coated bead-mediated proliferation of CD8+ T-cells, baseline vs PD: 78.7% vs 27.6%, *P*<0.01).

Summary/Conclusion:

Primary resistance to BsAbs is characterized by a higher proportion of T-cells expressing inhibitory receptors, a low T-cell/MM cell-ratio and Treg-driven immunosuppression, while reduced T-cell fitness due to continuous BsAb-mediated T-cell activation may contribute to development of acquired resistance.



Abbreviations: TEC, teclistamab; TAL, talquetamab; *P<0.05; ** P<0.01; *** P<0.001; **** P<0.0001.

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