The 11th World Congress on
CONTROVERSIES IN MULTIPLE MYELOMA (COMy)

Circulating Cytokines Correlate with Treatment Outcomes and CRS in Multiple Myeloma Patients Undergoing T-cell Engagers and CAR T-Cell Therapies

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Introduction

T-cell redirecting therapies, particularly bispecific T-cell engagers (TCEs) and chimeric antigen receptor T-cell (CAR-T) therapies, have revolutionized treatment regimens for refractory/relapsed multiple myeloma (RRMM) (1-3). However, most patients eventually experience relapse (4,5), and the main treatment-related toxicity, cytokine release syndrome (CRS), is significant (5-6). The role of circulating cytokines in assessing treatment outcomes and CRS in TCEs and CAR-T therapies remains largely underexplored.

This study is part of the immunoMMap project and aims to analyse cytokine profiles in RRMM patients undergoing TCEs or CAR-T therapies.

Methods

We measured 47 plasma cytokines in 30 RRMM patients treated with teclistamab, elranatamab, talquetamab, cevostamab, or ciltacabtagene autoleucel at baseline (Day 0, D0), and on Days 7, 14, 21, 30, 60, 90, 180, 270, and 360. Clinical characteristics of all patients are available upon request (STable 1). Cytokine levels were assessed using Bio-Plex® MAGPIX™ multiplex assay. Group comparisons were assessed using Mann-Whitney U test. Survival analyses were performed with the Kaplan-Meier method and compared using log-rank test. Associations between baseline (D0) cytokine levels and survival outcomes were evaluated using Cox proportional hazards models. Multivariate logistic regression was used to identify predictors of CRS.

Results

The spectra of peaked cytokines at corresponding time points differed between the TCE group (n=26) and the CAR-T group (n=4) (STable 2 available upon request). In TCE-treated patients, peak levels of 2 cytokines occurred on D0, 8 peaked on D7, 2 on D14, 2 on D21, while 33 cytokines showed no discernible peak. Cytokine levels most commonly peaked on Day 7, with representative patterns illustrated in **Figure 1.**

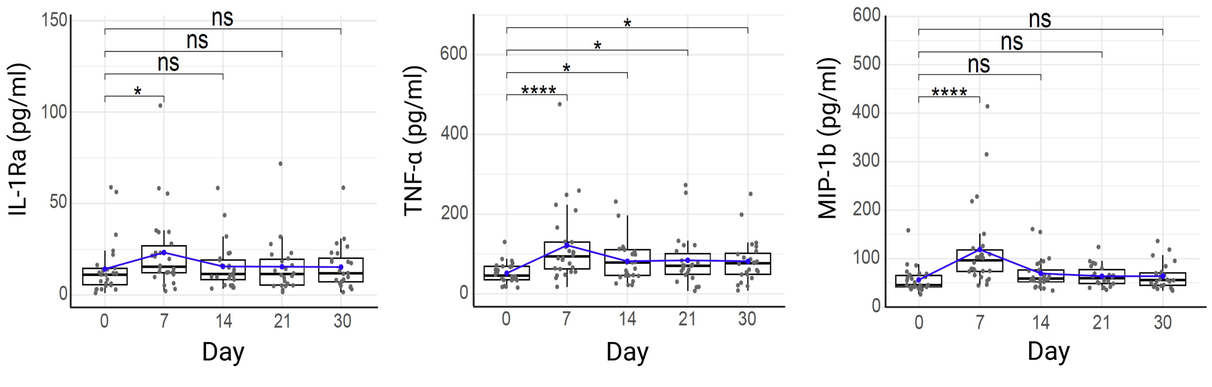

Figure 1. *Selected peaked cytokines (IL-1Rα, TNFα, MIP-1b) exhibited peaks on D7 in TCEs treated RRMM patients. *p<0.05, ****p<0.0001.*

To explore the association between cytokine dynamics and clinical response, we compared cytokine levels between responders (n = 21) and non-responders (n=9). Responders exhibited elevated T-cell differentiation-related factors, including IL-12p70 (D14, p<0.018), IL-4 (D7, p<0.027) and IL-9 (D7, D14, p<0.047), along with decreased inflammatory-related cytokines such as IL-18 (D0, D7, D21, p<0.044), TNF-α (D7, p<0.015), IL-6 (D30, p<0.048) and IL-8 (D21, p<0.01). Moreover, non-responders showed statistically higher levels of monocyte/macrophage and dendritic cells-recruiting cytokines, including MCP-1 (D7, D14, D21, D30, p<0.03), MIP-1α (D0, p<0.046), CXCL10/IP-10 (D7, p<0.019). Notably, the immunosuppressive cytokine IL-10, released by regulatory T-cells, was elevated in non-responders on D0, D7, and D21 (p<0.042). Meanwhile, responders exhibited significant increases in TNF-β (D14, p=0.01), which is associated with immune activation **(Figure 2)**.

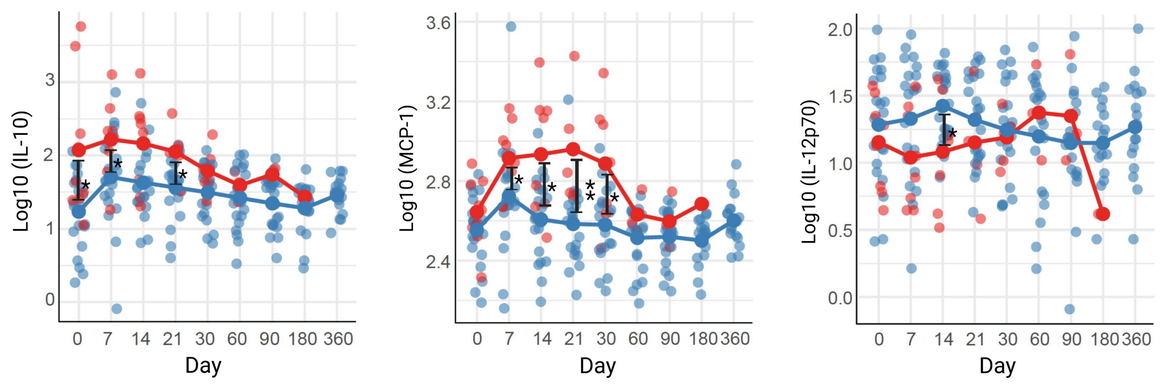

Figure 2. *Selected Significant different cytokine levels at multiple timepoints between responders (red) and non-responders (blue). *p<0.05, **p<0.01.*

When comparing 16 CRS patients with 14 non-CRS patients, we found higher levels of inflammatory-related cytokines and chemokines including IL-6 (D7, D21, p<0.044), IL-17F (D7, p<0.02), GRO-α (D7, D14, D30, p<0.03), as well as eosinophil activator IL-5 (D21, p<0.05) in CRS patients (**Figure 3**).

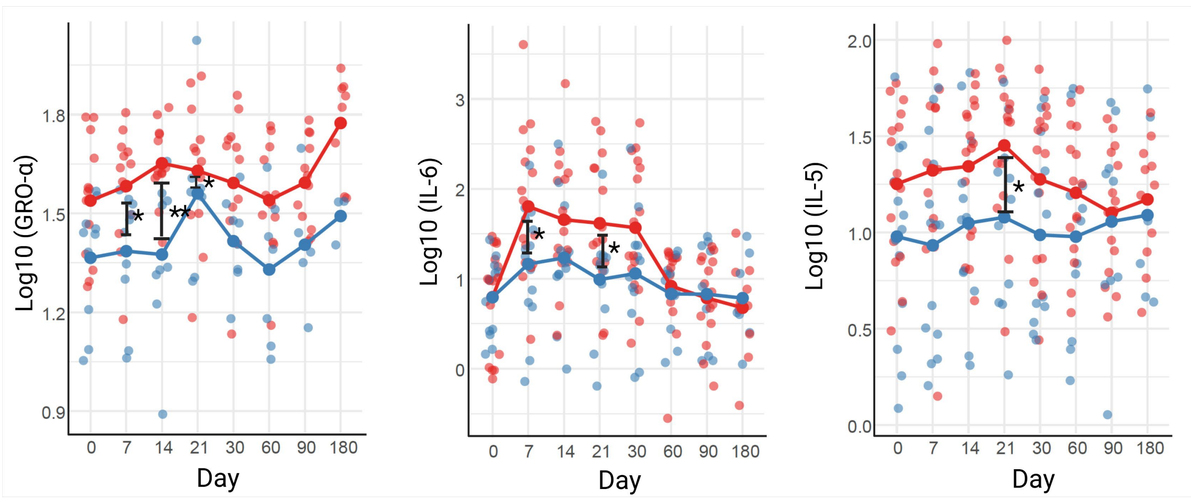

Figure 3. *Selected cytokines showing significant differences between CRS (red) and non-CRS (blue) patients at multiple timepoints. *p< 0.05, **p< 0.01.*

To evaluate the prognostic value of baseline cytokine levels, we performed univariate and multivariate analyses. In univariate analysis, elevated baseline MIP-1α, VEGF-A, MIG/CXCL9, and MIP-1β were associated with shorter progression-free survival (PFS). Similarly, higher baseline levels of IL-8, MIP-1α, TNF-α, VEGF-A, MIG/CXCL9 and MIP-1β, along with lower IL-10, were associated with shorter overall survival (OS). In multivariate Cox regression, MIP-1α was identified as an independent predictor of shorter PFS (HR=1.029, p=0.0044). Lower IL-10 and higher MIP-1α levels were independently associated with worse OS (HR=1.001, p<0.0001; HR=1.04, p=0.0005).

Finally, we analysed baseline cytokine levels to evaluate their association with CRS. IFN-γ was the only significant factor, with higher levels associated with CRS risk (OR=5.5, p=0.0281).

Conclusion

Longitudinal profiling of circulating cytokines revealed distinct immune signatures associated with treatment response, survival outcomes, and CRS in RRMM patients receiving TCEs or CAR-T therapies. These findings support the potential utility of cytokine-based biomarkers for risk stratification and early intervention.

References

1. Chari A, et al. *N Engl J Med.* 2022;387:2232–44.
2. Moreau P, et al. *N Engl J Med.* 2022;387:495–505.
3. San-Miguel J, et al. *N Engl J Med.* 2023;389:335–47.
4. Lee H, et al. *Blood.* 2024;143:1211–7.
5. Tao Z, et al. *Blood Cancer J.* 2024;14:213.
6. Géraud A, et al. *Eur J Cancer.* 2024;205:114075.

Acknowledgements

This work was supported by the European Union project LERCO (No. CZ.10.03.01/00/22_003/0000003), by the OP JAK SALVAGE project, co-financed by the EU and the State Budget; and by the Institutional support (MH CZ-DRO-FNOs/2024); (CZ.02.01.01/00/22_008/0004644).

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