The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

652.MULTIPLE MYELOMA: CLINICAL AND EPIDEMIOLOGICAL

Prolonged Cytopenia Following CAR T-Cell Therapy in Relapsed/Refractory Multiple Myeloma: A Prospective Comprehensive Biomarker Study

Xiang Zhou [1], Vivien Wagner [2], Emilia Stanojkovska [3], Christine Riedhammer [4], Xianghui Xiao, MD [5], Mara John [3], Lukas Scheller [6], Umair Munawar [7], Seungbin Han [8], Johannes M Waldschmidt, MD [5,9], Max S. Topp, MD [10], Johannes Duell, MD [11], Hermann Einsele, MD PhD [5], Angela Riedel, PhD [3], Martin Kortüm, MD [12], Leo Rasche, MD [5]

[1] Department of Internal Medicine II, University Hospital Wuerzburg, WüRzburg, Germany

[2] University of Wurzburg, Wurzburg, Germany

[3] Mildred Scheel Early Career Center for Cancer Research, University Hospital Wurzburg, Wurzburg, Germany

[4] Department of Internal Medicine II, University Hospital Wuerzburg, Würzburg, Germany

[5] Department of Internal Medicine II, University Hospital Würzburg, Würzburg, Germany

[6] University Hospital Wurzburg, Wuerzbzrg, DEU

[7] Department of Internal Medicine II, Department of Internal Medicine II, University Hospital WüRzburg, W, WüRzburg, Germany

[8] University Hospital Wurzburg, Wuerzburg, DEU

[9] Department of Medical Oncology, Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Boston, MA

[10] Medizinische Klinik Und Poliklinik II Universitätsklinikum Wurzburg, Wurzburg, Germany

[11] Department of Internal Medicine II, Hematology and Oncology, University Hospital Wuerzburg, Wuerzburg, Germany

[12] Mayo Clinic In Arizona, Scottsdale, AZ

Background

Chimeric antigen receptor (CAR) modified T-cells are leading to a paradigm shift in the treatment of relapsed/refractory (RR) multiple myeloma (MM). A high proportion of patients treated with CAR T-cells, however, experience prolonged cytopenia, with the mechanism remaining poorly understood. Here, we aimed to explore potential biomarkers that might correlate with cytopenia following CAR T-cell therapy in RRMM.

Methods

We prospectively collected peripheral blood (PB) of RRMM patients treated with idecabtagen-vicleucel (ide-cel) at the following time points: prior to lymphodepleting chemotherapy (LDC) (baseline), after ide-cel on day 4, 7, 14 and 28, and monthly thereafter. Cytopenia was determined according to the CTCAE version 5.0. Flow cytometry was performed with the following markers: CD45, CD3, CD4, CD8, CD62L, CD45RA, CD19, CD14, CD138, CD38 and a BCMA-CAR-detection marker.

Results

We included 222 PB samples at different sampling time points from 35 RRMM patients, who were pretreated with a median of 5 therapy lines (range 2-10). All patients were triple-class exposed and, 34 (97%) and 9 (26%) patients underwent autologous and allogeneic stem cell transplant (SCT), respectively.

First, we analyzed the relationship between baseline parameters and the duration of grade ≥ 3 cytopenia after ide-cel (n=35). Notably, patients who received allogeneic SCT or >4 lines of therapy did not develop longer lasting cytopenia than the remaining patients. We found a correlation between the baseline hemoglobin level and the duration of grade ≥ 3 anemia (r=-0.55, $P<0.001$). Similarly, low baseline platelet count indicated long duration of grade ≥ 3 thrombocytopenia (r=-0.48, $P=0.003$). Moreover, high baseline ferritin level correlated with long duration of grade ≥ 3 anemia (r=0.52, $P<0.001$) and thrombocytopenia (r=0.51, $P=0.002$). Furthermore, the maximum ferritin level after ide-cel was an indicator for long lasting grade ≥ 3 anemia (r=0.73, $P<0.001$) and thrombocytopenia (r=0.71, $P<0.001$). Interestingly, we found significant correlations between the duration of grade ≥ 3 lymphopenia and baseline CD4+ T-cell frequency (r=0.41, $P=0.02$), CD8+ T-cell frequency (r=-0.38, $P=0.04$) and CD4+/CD8+ ratio (r=0.4, $P=0.03$). Noteworthy, patients with β2-microglobulin level >3.5 mg/l displayed longer duration of grade ≥ 3 anemia (median: 9 vs 0 day, $P=0.007$) and neutropenia (median: 43 vs 12 days, $P=0.02$) compared with the remaining patients, suggesting that high tumor load might be a risk factor for prolonged cytopenia after ide-cel.

Second, we divided the follow-up PB samples (n=187) into two groups: early (<d60) and prolonged (≥d60) cytopenia to account for direct toxic effects related to LDC. A high ferritin level was associated with low hemoglobin level (<d60: r=-0.45, $P<0.001$, ≥d60: r=-0.62, $P<0.001$) and low platelet count (<d60: r=-0.58, $P<0.001$, ≥d60: r=-0.81, $P<0.001$) in both groups. In prolonged cytopenia (≥d60), lymphocyte count correlated with the T-cell count (r=0.7, $P<0.001$), suggesting that prolonged lymphopenia was mainly attributed to the reduced T-cell count after ide-cel. Of note, the frequency of naïve CD4+ T-cells (CD3+CD4+CD62L+CD45RA+) positively correlated with neutrophil count (r=0.58, $P<0.001$), hemoglobin level (r=0.37, $P=0.03$) and white blood cell count (r=0.5, $P=0.002$) in the ≥d60 group, suggesting that delayed immune reconstruction with reduced naïve CD4+ T-cells might contribute to prolonged cytopenia after ide-cel. Moreover, in the ≥d60 group, lymphocyte count was related with the frequency of CAR+CD4+ (r=-0.58, $P<0.001$), CAR+CD8+ (r=0.58, $P<0.001$), CAR-CD4+ (r=-0.72, $P<0.001$), CAR-CD8+ (r=0.75, $P<0.001$) T-cells, as well as the ratios of CAR+CD8+/CAR+CD4+ (r=-0.6, $P<0.001$) and CAR-CD8+/CAR-CD4+ (r=-0.75, $P<0.001$).

Conclusion

Here, we present one of the first prospective studies investigating the factors associated with prolonged cytopenia after CAR T-cell therapy in RRMM. High tumor load, preexisting cytopenia and high ferritin level are related with prolonged cytopenia after ide-cel. Delayed immune reconstruction, characterized by reduced naïve CD4+ T-cell count, indicates prolonged cytopenia following ide-cel therapy. Patients with high CD4+/CD8+ ratio are at risk of prolonged lymphopenia (with reduced T-cell count), which may be a risk factor for infectious complications and an issue for subsequent T-cell based immunotherapies.