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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

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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.

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