03. Diagnostic Challenges in Early CAR-T Cell Therapy Toxicities: Recognizing Mimics of Cytokine Release Syndrome (CRS) and Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)

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Background: Chimeric antigen receptor T-cell (CAR-T) therapy has significantly improved outcomes in relapsed and refractory hematologic malignancies. However, toxicities such as Cytokine release syndrome (CRS) and Immune effector cell associated neurotoxicity syndrome (ICANS) remain challenging. Several overlapping clinical conditions may mimic these toxicities and complicate early diagnosis, delay appropriate treatment and contribute to significant morbidity and mortality. **Aim:** The study aims to highlight important clinical conditions that mimic CRS and ICANS in the early post CAR-T period and discuss the diagnostic challenges associated with differentiating these conditions. **Methods:** A comprehensive analysis of clinical trials, observational studies and FAERS data was performed to evaluate the diagnostic mimics of CRS and ICANS and their incidence following CAR-T therapy. **Results:** CRS occurs in 49-95% of CAR-T recipients, with severe CRS in 1-24%, while ICANS develops in 12-60%, including severe cases in 3-50%. Bacterial sepsis is the dominant CRS mimic. Infectious mimics occur in 19-69% after CD19 CAR-T and 42-69% following BCMA CAR-T therapy. Hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) incidence ranges from 32.7-35.6% in anti-CD22 CAR-T trials. Studies have shown that neurotoxicity following CAR-T therapy manifests as ICANS accounting for 18.23% of cases, followed by Encephalopathy(5.40%), headache(5.24%), Aphasia(4.56%), Tremor(4.49%), Somnolence(3.15%), Depressed level of consciousness(2.29%), Seizures(2.12%) and Memory impairment(1.67%).Based on the reported incidence across clinical trials, approximately 1-2% of patients treated with CD19 CAR-T therapy develop cerebral edema. **Conclusion:** A substantial proportion of suspected early CAR-T toxicities represent alternative etiologies requiring distinct management. Systematic infectious, metabolic, neuroradiographic evaluation alongside cytokine profiling is essential. Recognition of mimics prevents inappropriate immunosuppression, optimizes targeted therapy and improves outcomes following cellular therapy.

Key Words: CAR-T cell therapy, Cytokine Release Syndrome (CRS), Chimeric Antigen, Neurotoxicity Syndromes, Hemophagocytic, Lymphohistiocytosis

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