Managing Myeloma

# *Updates in CRS and ICANS: Implications for the Emergency Department*

The advent of CAR T-cell therapies and bispecific antibodies (BsAbs) has significantly advanced the treatment of multiple myeloma (MM), leading to deep and durable remissions even in heavily pre-treated patients with relapsed or refractory disease. These innovative therapies have improved survival and increased the number of patients living with RRMM. However, the effectiveness of these treatments comes with challenges, notably serious adverse events like Cytokine Release Syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS). As more patients benefit from these therapies, the likelihood of encountering these complications increases, including in the Emergency Department (ED) setting, where CRS and ICANS can present with varied and often nonspecific symptoms, complicating diagnosis and management. This e-newsletter reviews key findings from the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting relative to CRS and ICANS associated with novel immunotherapies for MM, providing crucial insights into predicting, recognizing, and managing these immunotherapy-related adverse events.

## *Highlighted Abstract Summaries*

### Educating and Empowering Health Care Teams to Recognize and Intervene on Cytokine Release Syndrome and Immune Effector Cell-Associated Neurotoxicity Syndrome in Patients on Bispecific T-Cell Engager Therapy

***Authors:*** *Alessandra Petrillo, Woo Jin Seog, Justin Halterman, et al.*

This quality improvement study aimed to enhance the recognition and management of CRS and ICANS in patients undergoing BiTE therapy. The study focused on improving the knowledge of ED residents and attendings, as well as nurses, advanced practice providers, and hospitalists in the bone marrow transplant (BMT) unit at Stony Brook University Hospital. Baseline knowledge of CRS and ICANS was assessed using anonymous surveys before and after a 15-minute educational presentation. The results showed a significant increase in knowledge scores in both the ED (from 39% to 66%) and BMT department (from 45% to 68%) following the educational intervention. The study highlights the effectiveness of targeted education in addressing knowledge gaps and improving the management of these severe adverse events associated with BiTE therapies.

***Relevance:*** For practicing ED clinicians, this study underscores the critical importance of targeted education in improving the management of CRS and ICANS, which are significant complications of BiTE therapies. The study demonstrates that even brief, focused educational interventions can lead to substantial improvements in knowledge among healthcare providers. Given that CRS and ICANS can present with rapid onset and severe symptoms, enhanced awareness and preparedness are essential for timely and effective management. The improved recognition and response to these conditions can lead to improved patient outcomes and potentially reduce the need for more intensive emergency interventions. Future strategies, including the development of patient identification cards and centralized treatment protocols, aim to further support ED teams in managing these complex adverse events.

***Link:*** Abstract e23212

## Neurocognitive Testing to Predict ICANS Post-CAR T

***Authors:*** *William Wesson, Lauren Scott, Nahid Suleman, et al.*

This study aimed to determine whether neurocognitive testing could predict the incidence of ICANS in patients receiving CAR T-cell therapy. The research involved 360 patients who underwent CAR T therapy targeting CD19 or BCMA from December 2017 to December 2023. The study utilized two neurocognitive assessments: the St. Louis University Mental Status (SLUMS) Exam and the Montreal Cognitive Assessment (MoCA). The SLUMS exam and MoCA are designed to evaluate various levels of cognitive function, from normal cognition to severe impairment. Results indicated that while the SLUMS exam did not correlate with ICANS incidence, the MoCA showed a significant association. Specifically, patients with lower MoCA scores, indicating more severe cognitive impairment, had a higher incidence of ICANS. In contrast, higher MoCA scores were associated with a lower likelihood of developing ICANS. The study did not find a similar predictive value with SLUMS in patients receiving either CD19- or BCMA-directed CAR T therapy.

***Relevance:*** For practicing ED clinicians, this study provides important insights into the use of neurocognitive testing as a predictor for ICANS, a serious and potentially life-threatening complication of CAR T-cell therapy. While the SLUMS exam did not predict ICANS risk, the MoCA exam proved useful, with lower scores correlating with a higher incidence of severe ICANS. This suggests that patients with notable cognitive impairment prior to CAR T-cell therapy might be at increased risk for developing ICANS and may require closer monitoring. For ED clinicians, this information is critical for identifying high-risk patients early, ensuring timely and effective management of neurotoxicity symptoms. The ability to anticipate ICANS based on pre-treatment cognitive assessments can improve patient triage and intervention strategies, ultimately enhancing patient safety and care in the emergency setting.

***Link:*** Abstract e19003

## Early Prediction of Severe ICANS After Standard-of-Care CD19 CAR T-Cell Therapy Using Gradient-Boosted Classification Trees

***Authors:*** *Jennifer Jing Huang, Emily C. Liang, Aya Albittar, et al.*

This study demonstrates the use of the XGBoost machine learning algorithm to predict severe immune effector cell-associated neurotoxicity syndrome (ICANS) in patients undergoing standard-of-care CD19 CAR T-cell therapy. The study included 175 patients who received axicabtagene ciloleucel (axi-cel) or brexucabtagene autoleucel (brexu-cel). XGBoost was employed to analyze commonly available laboratory and vital sign data to predict the development of grade ≥3 ICANS, which occurred in 23.3% of patients. Key variables included serum ferritin levels on day +3, platelet counts on day 0 and day +3, patient age, IL-6 levels on day +3, and CRP levels. The XGBoost model achieved high predictive accuracy with an area under the receiver operating characteristic curve (AUROC) of 0.74, sensitivity of 0.95, and specificity of 0.90. Notably, elevated serum ferritin levels on day 0 and day +3 were strongly associated with severe ICANS. This predictive model allows for early identification of patients at high risk for severe ICANS and may support the development of prophylactic strategies.

***Relevance:*** For practicing ED clinicians, this study highlights the potential of using predictive models to anticipate severe ICANS in patients undergoing CAR T-cell therapy. The use of XGBoost to analyze laboratory and clinical data can help identify patients at high risk for developing severe ICANS before symptoms arise. This early identification is crucial for ED teams, as it allows for proactive management and preparation for potential complications. By incorporating predictive factors such as serum ferritin levels and platelet counts, ED clinicians can better anticipate and address severe neurotoxicity, improving patient outcomes and optimizing emergency care. The ability to identify high-risk patients

early can guide the implementation of targeted interventions and enhance readiness for managing ICANS, ultimately supporting safer and more effective care in the emergency setting.

***Link:*** Abstract 7034

## Longer-Term Follow-Up of Patients Receiving Prophylactic Tocilizumab for the Reduction of Cytokine Release Syndrome in the Phase 1/2 MajesTEC-1 Study of Teclistamab in Relapsed/Refractory Multiple Myeloma

***Authors:*** *Niels W.C.J. van de Donk, Alfred L. Garfall, Lotfi Benboubker, et al.*

This study investigated the effect of administering prophylactic tocilizumab (toci) prior to teclistamab, a bispecific antibody targeting BCMA×CD3, on the incidence of CRS in patients with RRMM. The analysis included 24 patients who received tocilizumab intravenously within 4 hours before the first teclistamab dose, with a median follow-up of 8.1 months. The results demonstrated a substantial reduction in the incidence of CRS compared to previous reports. Specifically, CRS occurred in 25% of patients, with all cases being of grades 1 or 2, and no instances of grade 3 or higher. The median time to onset of CRS was 2 days, and the median duration was 2 days, with all cases resolving without discontinuing teclistamab. The safety profile was consistent with earlier findings, with common adverse events including infections (79% of any grade; 25% grade 3/4), neutropenia (63%), and anemia (58%). Neurotoxic events were relatively rare, and no new safety signals emerged. The study supports the use of prophylactic tocilizumab as an effective measure to reduce CRS incidence and suggests that teclistamab may be safely administered in outpatient settings.

***Relevance:*** For practicing ED clinicians, this study highlights the significant benefit of prophylactic tocilizumab in reducing the incidence of CRS associated with teclistamab. The effective mitigation of CRS and the manageable nature of other adverse events suggest that teclistamab can potentially be administered in outpatient settings with reduced risk. This advancement may lead to fewer emergency admissions related to CRS, as prophylactic tocilizumab decreases the frequency and severity of this common complication. ED clinicians should be aware that while prophylaxis lowers CRS rates, vigilant monitoring remains crucial, especially for early identification and management of any residual or emerging adverse events. Understanding these developments can aid in optimizing patient care and preparedness for potential complications following bispecific antibody therapies.

***Link:*** Abstract 7517

## Ciltacabtagene Autoleucel in Patients with Lenalidomide-Refractory Multiple Myeloma: CARTITUDE-2 Cohort A Expansion Subgroup

***Authors:*** *Adam D. Cohen, Peter M. Voorhees, Thomas G. Martin, et al.*

This study evaluated the efficacy and safety of ciltacabtagene autoleucel (cilta-cel), a CAR T-cell therapy, in MM patients who are refractory to lenalidomide. The expansion subgroup of Cohort A included 24 patients who received cilta-cel with a median follow-up of 16 months. The results showed a high overall response rate (ORR) of 91%, with all evaluable patients achieving minimal residual disease negativity (MRD neg) at a sensitivity of 10–5. The median time to MRD negativity was 2 months, and 79% of responders maintained their response at 12 months. The 12-month progression-free survival (PFS) rate was 77%, and the overall survival (OS) rate was 91%.

Regarding safety, all patients experienced CRS, with 100% of cases being grades 1 or 2; the median time to CRS onset was 8 days, with recovery in 4 days. ICANS occurred in 17% of patients, with grades

ranging from 1 to 4; the median time to ICANS onset was 10 days and recovery took 2 days. Hematologic adverse events were common, including neutropenia in 96% of patients, and 35% of patients experienced infections, with one patient having a grade 5 infection due to sepsis. Two secondary malignancies were reported but were deemed not treatment-related.

***Relevance:*** For practicing ED clinicians, this study underscores the importance of anticipating and managing both CRS and ICANS in patients undergoing CAR T-cell therapy. Given the high incidence of CRS, even if predominantly low-grade, and the potential for severe neurotoxicities like ICANS, ED clinicians need to be prepared for prompt intervention. Understanding the typical onset and duration of these adverse events helps in effective triage and management. The high response rates and durable remissions associated with cilta-cel highlight its potential benefits, but they also necessitate vigilant monitoring for complications that could arise shortly after treatment, particularly in an emergency setting.

***Link:*** Abstract 7535

## *Importance of Staying Current with New Data*

As the field of multiple myeloma treatment continues to evolve, staying informed about the latest research and clinical advancements is crucial for optimizing patient care. The 2024 ASCO Annual Meeting has highlighted significant findings that can impact the management of CRS and ICANS. Integrating these insights into your clinical practice can enhance your ability to address and manage these challenging adverse events effectively.

We encourage you to visit the *Managing Myeloma* website to explore additional resources related to the latest advancements in myeloma care in the ED. By staying up-to-date with these developments, you can better navigate the complexities of novel immunotherapies and improve patient outcomes.

**The Role of the ED in Treating Multiple Myeloma in the Era of Novel Immunotherapies**

**Accredited Activity** **Podcast**

Thank you for engaging with this e-newsletter. We hope the information provided supports you in delivering cutting-edge care and managing the complexities of multiple myeloma in your practice.

## *References*

Alessandra Petrillo, et al. Educating and empowering health care teams who present to the hospital to recognize and intervene on cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) in patients on bispecific t-cell engager therapy (BiTEs): A quality improvement study. *JCO.* 2024. 42(16 suppl):e23212. DOI:10.1200/JCO.2024.42.16_suppl.e23212

William Wesson, et al. Neurocognitive testing to predict ICANS post-CAR T. *JCO.* 2024.42(16 suppl):e19003. DOI:10.1200/JCO.2024.42.16_suppl.e19003

Jennifer Jing Huang, et al. Early prediction of severe ICANS after standard-of-care CD19 CAR T-cell therapy using gradient-boosted classification trees. *JCO.* 2024. 42(16 suppl): 7034. DOI:10.1200/JCO.2024.42.16_suppl.7034

Niels W.C.J. van de Donk, et al. Longer-term follow-up of patients (pts) receiving prophylactic tocilizumab (toci) for the reduction of cytokine release syndrome (CRS) in the phase 1/2 MajesTEC-1 study of teclistamab in relapsed/refractory multiple myeloma (RRMM). *JCO.* 2024. 42(16 suppl):7517. DOI:10.1200/JCO.2024.42.16_suppl.7517

Adam D. Cohen, et al. Ciltacabtagene autoleucel in patients with lenalidomide-refractory multiple myeloma: CARTITUDE-2 cohort A expansion subgroup. *JCO.* 2024. 42(16 suppl):7535. DOI:10.1200/JCO.2024.42.16_suppl.7535

Provided by MediCom Worldwide, Inc.
Supported by an educational grant from Janssen Biotech, Inc. administered by Janssen Scientific Affairs, LLC.