CAR-T Cell Therapy Recipients Admitted to the ICU

Subjects: Critical Care Medicine

Contributor: Catalin Constantinescu , Vlad Moisoiu , Bogdan Tigu , David Kegyes , Ciprian Tomuleasa

To better understand immunotherapy-related complications from an ICU standpoint, acknowledge the deteriorating patient on the ward, reduce the intensive care unit (ICU) admission rate, advance ICU care, and improve the outcomes of these patients, a standard of care and research regarding CAR-T cell-based immunotherapies should be created.

intensive care critical illness CAR-T cell

1. Background

Immunotherapy with chimeric antigen receptor (CAR)-T cell is expanding in the field of hematology [1][2][3] and has gained much attention in recent years. Along with the administration of these immunotherapies, complications also arise, the most common ones being cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), which, when severe, often require admission and complex management into an intensive care unit (ICU) [4][5][6][7].

Most studies that describe patients who were treated with CAR-T cell therapy have analyzed the clinical experience from the starting point of lymphodepletion until the very end of treatment but with limited information given regarding the patients who were admitted to the ICU with no mention of the resources used or required life-saving interventions that could have improved their different outcomes. Therefore, the information concerning this segment of practice is scarce [8]. Current ICU practices in CAR-T cell recipients admitted to the ICU are deduced from the general ICU population and are not individualized accordingly.

As intensive care physicians, it is important to acknowledge the currently available information and experiences of the other medical specialties regarding immunotherapies and contribute by creating a standard of care for future ICU patients treated with CAR-T cell therapy. It is mandatory to have know-how regarding the CAR products available, toxicities observed, and available treatment of toxicities, and to update ourselves with the specifics of practices and interventions applicable within the ICU when caring for critically ill CAR patients.

2. Outcomes of CAR-T Cell Therapy Recipients Admitted to the ICU

Given the matter that around one-third of the total recipients of CAR-T cells required ICU admission, it represents an important fact to remember that highlights the need to have an available bed or dedicated high-dependency unit with trained medical personnel. Even though the incidence of ICU admission showed a substantial level of heterogeneity among the studies (I^2 of 80%), this rate of admission was similar to the one mentioned in the literature [6][9][10]. Moreover, the readmission rate to the ICU within 30 days was around 18%, which suggests that physicians should expect readmission after an initial successful recovery in a significant proportion of patients. Reasons for readmission are not mentioned in the assessed studies, but they should be clearly stated for clinical and economic purposes.

Major reasons for ICU admission for patients treated with CAR-T cell are the development of CRS and ICANS, associated sepsis, single or multiple organ failure, hemophagocytic lymphohistiocytosis, stroke, and difficult airway management (bulky cervical or mediastinal lymphadenopathy, and tumor infiltration) [11][12]. CRS and ICANS were present in a third of these patients at the moment of admission to the ICU. Hypotension, altered mental status, AKI, and acute respiratory failure were the main reasons for ICU admission in these studies. This underlines that hematologists should carefully assess these patients daily on the wards for neurological, respiratory, cardiovascular, and kidney organ failure. Usually, the patients deteriorate clinically over time, and there is a failure to identify the process [13][14]. A delay in admission to the ICU and more than one organ failure are associated with increased mortality [15][16]. Validated scores such as MEWS/NEWS should be used daily by the medical personnel to assess the patients on the ward, and with the help of these, early admission to the ICU could be suggested [17][18][19].

CRS is a complication of CAR-T cell treatment. Hypotension, AKI, arrhythmias, and fever are the most frequent signs and symptoms of CRS presentation. The presence of these signs and symptoms should prompt physicians to do a thorough screening for CRS, which could lead to organ failure if not taken care of. Noteworthy, the same signs and symptoms could be present in sepsis, so it is worth remembering that sepsis is a differential diagnosis when dealing with CRS. A comprehensive sepsis screening should rapidly follow with the institution of sepsis treatment if suspected [20][21]. The lymphodepletion regimen given prior to CAR-T cell therapy leads to immunosuppression, which can lead to bacterial infections. Patients with immunosuppression and CAR–T cell-associated toxicities have the highest risk for infection, which is reported to be around 23–43% during the first month after CAR-T therapy infusion [22][23]. Cytokine identification could be used to differentiate between CRS and sepsis.

The most required interventions initiated in ICU in CAR-T cell recipients were high-flow nasal oxygen or noninvasive ventilation, invasive mechanical ventilation, infusion of vasoactive drugs, and a small proportion even required renal replacement therapy (RRT) during ICU stay. Notable, while AKI was one of the main reasons for ICU admission and one of the main signs of CRS presentation, RRT was only required in a low percentage of cases. The lack of diagnostic criteria for AKI within the assessed manuscripts makes it impossible to make assumptions. Future studies should focus on what is the real percentage of patients presenting with AKI and which one of the patients could be helped by initiating RRT early. RRT with Cytosorb® or other hemadsorbers can be used as a

bridge therapy for refractory CRS, as well as for managing sepsis, due to the elimination/adsorption of cytokines through the filter [24][25].

The mean length of hospital stay was around 22 days, ICU stay around 5 days, and admission to the intensive care after CAR-T infusion was around 5 days, so physicians should expect a relatively long duration of hospital stay, which increases costs.

A mean SOFA value of 4.5 calculated at the admission moment corresponds to a mortality of around 15–20%, according to the literature [26][27]. Hematologic patients are considered to be a frail patient population [16][28]. Putting these two facts together, there is a suggestion that there is an increased risk of mortality among hematologic patients treated with CAR-T cells, even though the reported mortality of CAR-T cell recipients admitted to the ICU is around 6%, which could be considered low. A deeper look into this finding is required due to the fact that the mortality rate is disease, treatment, or sepsis-related, and the SOFA calculated in the mentioned studies is not solely performed on oncohematological patients. By having a dedicated team, environment, guidelines, and standard of care, the rate of detection of complications can increase, and earlier treatment started, which could improve the overall survival rate.

The focus of ICU management of these patients should reside on several problems. For an optimal management strategy in cases of respiratory failure, a lung protective strategy and a review of chest and neck imaging in the hematologic population should become standard practice to avoid airway emergencies and adverse outcomes. Regarding fluid management, goal-directed fluid therapy should be followed and helped by the use of performing point-of-care cardiac and lung ultrasound to guide it [29]. The choice of the most appropriate intravenous fluid, like crystalloids or colloids, and the use of vasoactive agents remain to be studied in the setting of pulmonary capillary leak, CRS-related cardiomyopathy, or oliguric renal failure [30]. Unfortunately, when sepsis is present in these patients, there are arguments that it is correlated with the risk of particularly poor outcomes [31]. This suggests that a comprehensive search for the site of infections is mandatory.

Studies that focus on death from the progression of the disease in contrast to death from toxicity of treatment will have to be conducted to establish the incriminating factors. While immunotherapies are in continuous development, with newer CAR-T cell therapies entering the market, the indications for this treatment could become broader [1][32]. Toxicities and complications magnitude will have to be considered and anticipated because, at the moment, they are difficult to predict.

Earlier admission to the ICU or high dependency unit (HDU) of patients at high risk of CRS might also improve outcomes, as seen in previous studies on hematological malignancies, and might paradoxically reduce the duration of stay in the ICU [33]. Having a hematological pathology does not seal access to an ICU, and it does not mean there are no benefits if hospitalized in the ICU, as many might think. The current risk stratification models in the context of immunotherapies are limited. There is not a single perfect tool for early prediction for ICU admission, but by adopting different scores like MEWS/NEWS and having a second opinion from an ICU physician, the threshold

for admission could be set lower. Risk prediction models in the context of critically ill patients following immunotherapies could be developed by using clinical prediction models or machine learning algorithms.

There is a dire need to create a standard of care and research to change and improve the current practice, with approaches focusing on reducing the incidence of CRS and ICANS, the need for ICU admission, early sepsis screening, antimicrobial prophylaxis, and research on management strategies to enhance the care of critically ill patients following CAR-T cell therapy, characterization of the clinical course for future prevention planning, all of which work to improve the overall outcomes and increase the quality of life of these patients.

The endless opportunities that immunotherapy has to offer pose a challenge to both hematologists and intensive care physicians. The future is pictured as a worldwide standard of care as ICU management becomes integrated with overall treatment opportunities. More clinical trials are required to address the current state of things, with trials that should also address the different CAR-T therapies available.

References

1. Wang, Z.; Wu, Z.; Liu, Y.; Han, W. New development in CAR-T cell therapy. J. Hematol. Oncol. 2017, 10, 53.
2. Zhang, X.; Zhu, L.; Zhang, H.; Chen, S.; Xiao, Y. CAR-T Cell Therapy in Hematological Malignancies: Current Opportunities and Challenges. Front. Immunol. 2022, 13, 927153.
3. Abramson, J.S.; Palomba, M.L.; Gordon, L.I.; Lunning, M.A.; Wang, M.; Arnason, J.; Mehta, A.; Purev, E.; Maloney, D.G.; Andreadis, C.; et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): A multicentre seamless design study. Lancet 2020, 396, 839–852.
4. Morris, E.C.; Neelapu, S.S.; Giavridis, T.; Sadelain, M. Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy. Nat. Rev. Immunol. 2022, 22, 85–96.
5. Chou, C.K.; Turtle, C.J. Insight into mechanisms associated with cytokine release syndrome and neurotoxicity after CD19 CAR-T cell immunotherapy. Bone Marrow Transplant. 2019, 54, 780–784.
6. Maude, S.L.; Laetsch, T.W.; Buechner, J.; Rives, S.; Boyer, M.; Bittencourt, H.; Bader, P.; Verneris, M.R.; Stefanski, H.E.; Myers, G.D.; et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N. Engl. J. Med. 2018, 378, 439–448.
7. Chavez, J.C.; Jain, M.D.; Kharfan-Dabaja, M.A. Cytokine release syndrome and neurologic toxicities associated with chimeric antigen receptor T-Cell therapy: A comprehensive review of emerging grading models. Hematol. Oncol. Stem Cell Ther. 2020, 13, 1–6.

8. Brown, A.R.T.; Jindani, I.; Melancon, J.; Erfe, R.; Westin, J.; Feng, L.; Gutierrez, C. ICU Resource Use in Critically Ill Patients Following Chimeric Antigen Receptor T-Cell Therapy. Am. J. Respir. Crit. Care Med. 2020, 202, 1184–1187.
9. Neelapu, S.S.; Locke, F.L.; Bartlett, N.L.; Lekakis, L.J.; Miklos, D.B.; Jacobson, C.A.; Braunschweig, I.; Oluwole, O.O.; Siddiqi, T.; Lin, Y.; et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N. Engl. J. Med. 2017, 377, 2531–2544.
10. Schuster, S.J.; Bishop, M.R.; Tam, C.S.; Waller, E.K.; Borchmann, P.; McGuirk, J.P.; Jäger, U.; Jaglowski, S.; Andreadis, C.; Westin, J.R.; et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N. Engl. J. Med. 2019, 380, 45–56.
11. Cordeiro, A.; Bezerra, E.D.; Hirayama, A.V.; Hill, J.A.; Wu, Q.V.; Voutsinas, J.; Sorror, M.L.; Turtle, C.J.; Maloney, D.G.; Bar, M. Late Events after Treatment with CD19-Targeted Chimeric Antigen Receptor Modified T Cells. Biol. Blood Marrow Transplant. 2020, 26, 26–33.
12. Burns, E.A.; Gentille, C.; Trachtenberg, B.; Pingali, S.R.; Anand, K. Cardiotoxicity Associated with Anti-CD19 Chimeric Antigen Receptor T-Cell (CAR-T) Therapy: Recognition, Risk Factors, and Management. Diseases 2021, 9, 20.
13. Van Vliet, M.; Verburg, I.W.M.; van den Boogaard, M.; de Keizer, N.F.; Peek, N.; Blijlevens, N.M.A.; Pickkers, P. Trends in admission prevalence, illness severity and survival of haematological patients treated in Dutch intensive care units. Intensive Care Med. 2014, 40, 1275–1284.
14. Hampshire, P.A.; Welch, C.A.; McCrossan, L.A.; Francis, K.; Harrison, D.A. Admission factors associated with hospital mortality in patients with haematological malignancy admitted to UK adult, general critical care units: A secondary analysis of the ICNARC Case Mix Programme Database. Crit. Care 2009, 13, R137.
15. Mokart, D.; Lambert, J.; Schnell, D.; Fouché, L.; Rabbat, A.; Kouatchet, A.; Lemiale, V.; Vincent, F.; Lengliné, E.; Bruneel, F.; et al. Delayed intensive care unit admission is associated with increased mortality in patients with cancer with acute respiratory failure. Leuk. Lymphoma 2013, 54, 1724–1729.
16. De Vries, V.A.; Müller, M.C.A.; Arbous, M.S.; Biemond, B.J.; Blijlevens, N.M.A.; Kusadasi, N.; Span, L.R.F.; Vlaar, A.P.J.; van Westerloo, D.J.; Kluin-Nelemans, H.C.; et al. Long-Term Outcome of Patients with a Hematologic Malignancy and Multiple Organ Failure Admitted at the Intensive Care. Crit. Care Med. 2019, 47, e120–e128.
17. Mitsunaga, T.; Hasegawa, I.; Uzura, M.; Okuno, K.; Otani, K.; Ohtaki, Y.; Sekine, A.; Takeda, S. Comparison of the National Early Warning Score (NEWS) and the Modified Early Warning Score (MEWS) for predicting admission and in-hospital mortality in elderly patients in the pre-hospital setting and in the emergency department. PeerJ 2019, 7, e6947.

18. Constantinescu, C.; Bodolea, C.; Pasca, S.; Teodorescu, P.; Dima, D.; Rus, I.; Tat, T.; Achimas-Cadariu, P.; Tanase, A.; Tomuleasa, C.; et al. Clinical Approach to the Patient in Critical State Following Immunotherapy and/or Stem Cell Transplantation: Guideline for the On-Call Physician. J. Clin. Med. 2019, 8, 884.
19. Constantinescu, C.; Pasca, S.; Iluta, S.; Gafencu, G.; Santa, M.; Jitaru, C.; Teodorescu, P.; Dima, D.; Zdrenghea, M.; Tomuleasa, C. The Predictive Role of Modified Early Warning Score in 174 Hematological Patients at the Point of Transfer to the Intensive Care Unit. J. Clin. Med. 2021, 10, 4766.
20. Valade, S.; Darmon, M.; Zafrani, L.; Mariotte, E.; Lemiale, V.; Bredin, S.; Dumas, G.; Boissel, N.; Rabian, F.; Baruchel, A.; et al. The use of ICU resources in CAR-T cell recipients: A hospital-wide study. Ann. Intensive Care 2022, 12, 75.
21. Evans, L.; Rhodes, A.; Alhazzani, W.; Antonelli, M.; Coopersmith, C.M.; French, C.; Machado, F.R.; Mcintyre, L.; Ostermann, M.; Prescott, H.C.; et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021, 47, 1181–1247.
22. Hill, J.A.; Li, D.; Hay, K.A.; Green, M.L.; Cherian, S.; Chen, X.; Riddell, S.R.; Maloney, D.G.; Boeckh, M.; Turtle, C.J. Infectious complications of CD19-targeted chimeric antigen receptor–modified t-cell immunotherapy. Blood 2018, 131, 121–130.
23. Wittmann Dayagi, T.; Sherman, G.; Bielorai, B.; Adam, E.; Besser, M.J.; Shimoni, A.; Nagler, A.; Toren, A.; Jacoby, E.; Avigdor, A. Characteristics and risk factors of infections following CD28-based CD19 CAR-T cells. Leuk. Lymphoma 2021, 62, 1692–1701.
24. Constantinescu, C.; Pasca, S.; Tat, T.; Teodorescu, P.; Vlad, C.; Iluta, S.; Dima, D.; Tomescu, D.; Scarlatescu, E.; Tanase, A.; et al. Continuous renal replacement therapy in cytokine release syndrome following immunotherapy or cellular therapies? J. Immunother. Cancer 2020, 8, e000742.
25. Bottari, G.; Lorenzetti, G.; Severini, F.; Cappoli, A.; Cecchetti, C.; Guzzo, I. Role of Hemoperfusion With CytoSorb Associated with Continuous Kidney Replacement Therapy on Renal Outcome in Critically Ill Children with Septic Shock. Front. Pediatr. 2021, 9, 718049.
26. Cárdenas-Turanzas, M.; Ensor, J.; Wakefield, C.; Zhang, K.; Wallace, S.K.; Price, K.J.; Nates, J.L. Cross-validation of a sequential organ failure assessment score-based model to predict mortality in patients with cancer admitted to the intensive care unit. J. Crit. Care 2012, 27, 673–680.
27. Vincent, J.L.; de Mendonça, A.; Cantraine, F.; Moreno, R.; Takala, J.; Suter, P.M.; Sprung, C.L.; Colardyn, F.; Blecher, S. Use of the SOFA Score to assess the incidence of organ dysfunction/failure in intensive care units: Results of a Multicenter, Prospective Study. Working group on “sepsis-related problems” of the European Society of Intensive Care Medicine. Crit. Care Med. 1998, 26, 1793–1800.

28. Oeyen, S.G.; Benoit, D.D.; Annemans, L.; Depuydt, P.O.; Van Belle, S.J.; Troisi, R.I.; Noens, L.A.; Pattyn, P.; Decruyenaere, J.M. Long-term outcomes and quality of life in critically ill patients with hematological or solid malignancies: A single center study. Intensive Care Med. 2013, 39, 889–898.
29. Lichtenstein, D.A. BLUE-protocol and FALLS-protocol: Two applications of lung ultrasound in the critically ill. Chest 2015, 147, 1659–1670.
30. Martin, G.S.; Bassett, P. Crystalloids vs. colloids for fluid resuscitation in the Intensive Care Unit: A systematic review and meta-analysis. J. Crit. Care 2019, 50, 144–154.
31. Azoulay, É.; Castro, P.; Maamar, A.; Metaxa, V.; de Moraes, A.G.; Voigt, L.; Wallet, F.; Klouche, K.; Picard, M.; Moreau, A.-S.; et al. Outcomes in patients treated with chimeric antigen receptor T-cell therapy who were admitted to intensive care (CARTTAS): An international, multicentre, observational cohort study. Lancet Haematol. 2021, 8, e355–e364.
32. Sermer, D.; Brentjens, R. CAR T-Cell Therapy: Full speed ahead. Hematol. Oncol. 2019, 37 (Suppl. S1), 95–100.
33. Benoit, D.D.; Depuydt, P.O.; Vandewoude, K.H.; Offner, F.C.; Boterberg, T.; De Cock, C.A.; Noens, L.A.; Janssens, A.M.; Decruyenaere, J.M. Outcome in severely ill patients with hematological malignancies who received intravenous chemotherapy in the intensive care unit. Intensive Care Med. 2006, 32, 93–99.