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Editorial

After CAR-T therapy for myeloma: challenge of persistent cytopenias and infections

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The authors declare no competing interests.

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The advent of CAR-T cell therapy represents a dramatic breakthrough in the management of relapsed/refractory multiple myeloma (RRMM), offering hope to patients exhausted with multiple lines of treatment. Two CAR-T products ide-cel and cilta-cel received endorsement from the U.S. Food and Drug Administration and the European Medicines Agency in 2021 and 2022, based on results of pivotal KarMMa and CARTITUDE-1 trials that were the first to demonstrate remarkable efficacy of these products. However, these studies also underscored the significant risk of cytopenias and infections, common adverse events presenting compelling clinical challenges.

In the current issue of Haematologica, Dima *et al*. report results of a multicenter retrospective study, providing much-awaited insights into short- and long-term hematological and infectious complications associated with cilta-cel, based on the data obtained outside the setting of controlled clinical trials[1]. The study findings were quite sobering: over half of the patients experienced severe cytopenias at day 30 post-infusion, with nearly a quarter of them remaining affected at day 90. Similarly, in an earlier study by the same group, treatment with standard-of-care (SOC) ide-cel appeared to be associated with severe cytopenias documented in 58% and 31% of patients at days 30 and 90, respectively[2]. Such persistence of cytopenias emphasizes the need for close monitoring and consideration of supportive care application well beyond the initial treatment period. The identified risk factors for severe cytopenia included baseline extramedullary disease, high-risk cytogenetics, more than four lines of prior therapy, existing cytopenia at apheresis or pre-lymphodepletion, a high CAR-HEMATOTOX score, and tocilizumab use. While the pathophysiology of long-term cytopenia is considered multifactorial, the recently reported evidence suggests that B-cell maturation antigen (BCMA) CAR-T cells may exert a paracrine effect on the differentiation of hematopoietic stem and progenitor cells, promoting the development of more immature cell phenotypes[3]. Not unexpectedly, findings of a recently published analysis unequivocally demonstrate that persistent cytopenias, especially anemia and neutropenia, occurring at various time points following BCMA therapy in RRMM patients, portend a poor prognosis, as reflected by significantly reduced progression-free survival and overall survival[4].

The study by Dima *et al*. also explored immunity changes following cilta-cel administration and analyzed the use of essential supportive therapies, including granulocyte colony-stimulating factor (65% of patients), blood transfusion (38%), thrombopoietin agonists (10%), and a $CD34^+$ stem cell boost (9.5%). Importantly, among patients receiving a stem cell boost (n=10), all except one responded to the therapy, with a median time to hematological recovery of 21 (range: 6-96) days. These findings further support the value of this approach, particularly in MM, where many patients have stem cells available for reinfusion.

Infections are another well-recognized hallmark complication, associated with CAR-T cell therapy. In this context, data from a large systematic review and meta-analysis, assessing comparative incidence and causes of non-relapse mortality (NRM) following CAR-T cell therapy in patients with a broad spectrum of hematological malignancies, look particularly alarming. Among 574 reported non-relapse deaths, over half were attributed to infections, with the highest NRM seen in mantle cell lymphoma (10.6%) and MM (8%)[5]. In the aforementioned former trial by the same group, comparing efficacy, safety and survival rates of SOC cilta-cel versus ide-cel using inverse probability of treatment weighting, patients receiving cilta-cel were found to be more likely to experience an infection (47% in cilta-cel and 35% in ide-cel)[2]. In the study by Dima *et al.*, nearly half of the patients treated with cilta-cel developed infections, with up to one third of the cases classified as severe. Noteworthy, but not surprisingly, there was a temporal shift in the incidence of different infection types, with even distribution of early-onset events (up to day 30 post-injection) between bacterial and viral infections and predominance of viral pathogens in the later period, suggesting evolving immune vulnerabilities following CAR-T cell therapy. The study included heavily pretreated, refractory, or relapsed MM patients, a population inherently at high risk for infections, with severe infections reported in a significant proportion of cases during therapy and a cumulative infection risk exceeding 65% over the disease course[6-8]. This risk reflects both disease-related immunodeficiency and cumulative immunosuppression resulting from prior treatments. While it is hardly possible to determine to what extent infections diagnosed in patients incorporated

in this study were specifically attributed to CAR-T therapy and its associated cytopenias, better understanding of the overall risk and predictors of infections in this vulnerable patient category remains essential. This leaves the hematology community with a pressing need for reliable risk stratification models, enabling prompt identification of patients who would benefit from preemptive interventions. The association of severe infections with poor performance status, higher grade of cytokine release syndrome, delayed neurotoxicity, immunosuppressive therapy, and hypogammaglobulinemia, demonstrated in the study by Dima *et al*., could provide a basis for the development of such tools.

Finally, the current study investigated the immunity status in a subset of patients following cilta-cel administration. This issue still remains a gray area and many institutions intuitively support post-CAR-T cell vaccination. In this study, antibody level analysis revealed loss of humoral immunity to herpes simplex virus (8% of 24 patients) and varicella zoster virus (14% of 24 patients). Notably, 42% of patients lost immunity to pneumococcus in at least one of 14 evaluated IgG antibody titers. While these findings contribute valuable information, the small sample size and the apparently lower extent of immunity loss compared to hematopoietic cell transplant recipients[9] emphasize the need for further evidence to fully guide revaccination strategies following this treatment.

As cilta-cel and other CAR-T cell therapies become increasingly integrated into standard practice, these findings reinforce the imperative for robust, multidisciplinary care models. Early identification of high-risk patients, proactive infection surveillance, and aggressive management of cytopenias are crucial. Furthermore, ongoing research of mechanisms of prolonged cytopenias and immune dysfunction may yield targeted strategies to mitigate these risks. To that end, the journey with cilta-cel does not end at infusion; it extends through months of careful observation, interventions, and adaptation. This study is a timely reminder that potentials of CAR-T therapy need to be balanced with a commitment to efficiently manage its long-term toxicities.

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Figure legend:

The CAR-T Road: Cytopenias and Infections Over Time

Following CAR-T infusion, over 50% of patients experience severe cytopenias by day 30. This rate declines to 20-40% by day 90, with most cases resolving by day 180. Infections are common, affecting approximately 50% of patients post-infusion. Early infections are predominantly viral and occur within the first 30 days. Late severe infections are less frequent, affecting around 10% of patients. This figure was created using Canva.

Risk factors for severe cytopenia:

- Extramedullary disease
- High-risk cytogenetics
- >4 prior lines of therapy
- Existing cytopenia at apheresis or pre-lymphodepletion
- High CAR-HEMATOTOX score
- Tocilizumab