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

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The advent of chimeric antigen receptor (CAR) T-cell therapy represents a dramatic breakthrough in the management of relapsed/refractory multiple myeloma (MM), offering hope to patients exhausted by multiple lines of treatment. Two CAR T-cell products idecabtagene vicleucel (ida-cel) and ciltacabtagene autoleucel (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 the pivotal KarMMa and CARTITUDE-1 trials, which 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 creating 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 hematologic and infectious complications associated with cilta-cel, based on the data obtained outside the setting of controlled clinical trials.[1] The study's findings were quite sobering: over half of the patients experienced severe cytopenias at day 30 after infusion, with nearly a quarter of them remaining affected at day 90 (Figure 1). Similarly, in an earlier study by the same group, treatment with standard-of-care 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 the application of supportive care 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 before lymphodepletion, a high CAR-HEMATOTOX score, and tocilizumab use (Figure 1).

While the pathophysiology of long-term cytopenia is considered multifactorial, 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 timepoints following BCMA therapy in relapsed/refractory MM 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 hematologic recovery of 21 days (range, 6-96 days). These findings further support the value of this approach, particularly in MM, in which 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 the comparative incidence and causes of non-relapse mortality following CAR T-cell therapy in patients with a broad spectrum of hematologic malignancies, look particularly alarming. Among 574 reported non-relapse deaths, over half were attributed to infections, with the highest non-relapse mortality 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 standard-of-care 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 those receiving cilta-cel and 35% in those receiving ide-cel). [2] In the study by Dima *et al.*, nearly half of the patients treated with cilta-cel developed

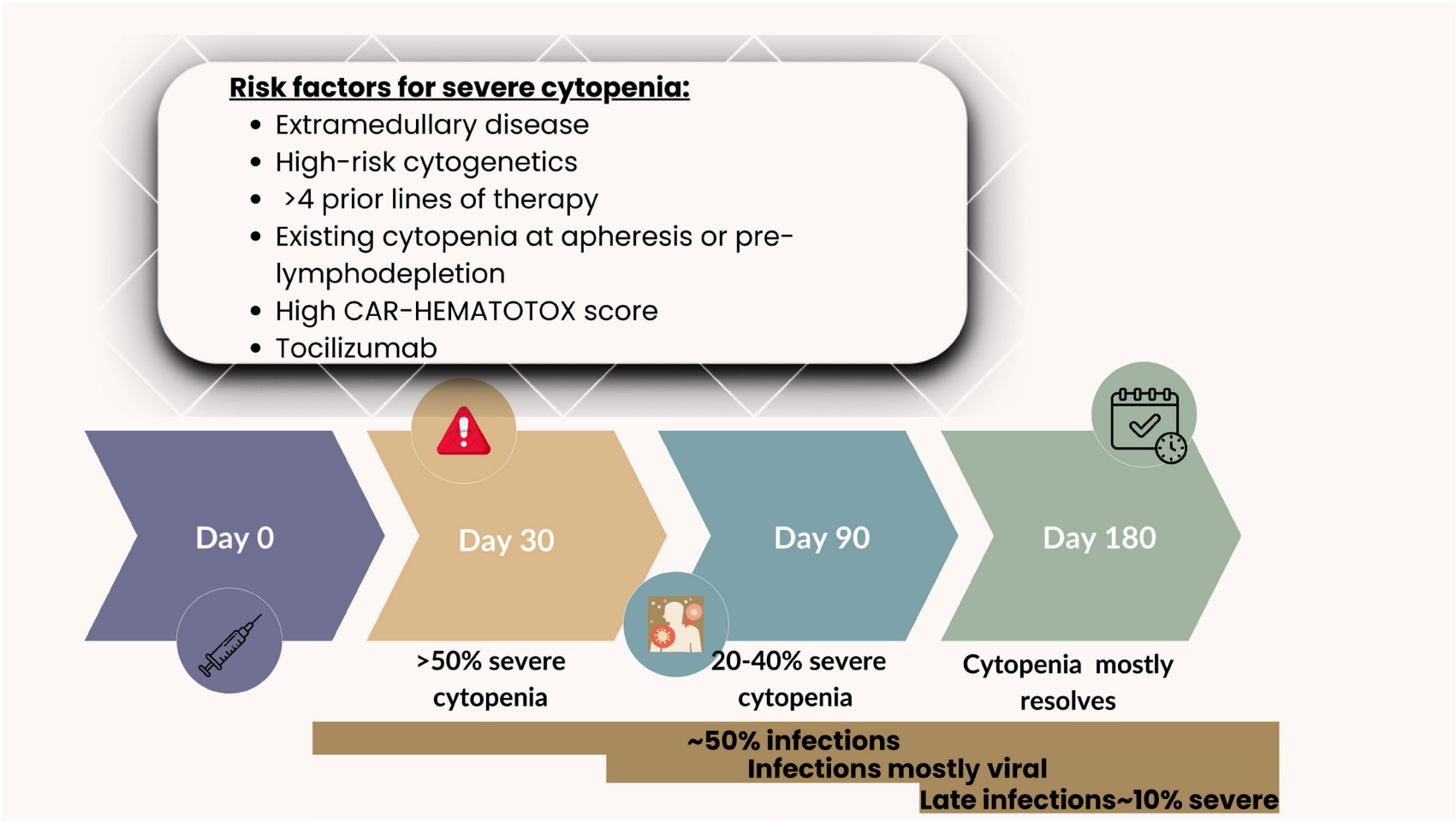

Figure 1. The chimeric antigen receptor T-cell road: cytopenias and infections over time. Following the infusion of chimeric antigen receptor T cells, over 50% of patients experience severe cytopenias by day 30. This rate declines to 20-40% by day 90, with most cases resolving by day 180. Infections are common, affecting approximately 50% of patients after infusion. Late severe infections are less frequent, affecting around 10% of patients. This figure was created using Canva.

infections, with up to one third of the cases classified as severe. It is noteworthy, but not surprising, that there was a temporal shift in the incidence of different types of infection, with an even distribution of early-onset events (up to day 30 after injection) between bacterial and viral infections and predominance of viral pathogens in the later period, suggesting evolving immune vulnerabilities following CAR T-cell therapy (Figure 1). The study included heavily pretreated, refractory, or relapsed MM patients, a population inherently at high risk of 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 included in this study were specifically attributable to CAR T-cell therapy and its associated cytopenias, better understanding of the overall risk and predictors of infections in this vulnerable category of patients 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 pre-emptive 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 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 the potentials of CAR T-cell therapy need to be balanced with a commitment to efficiently manage its long-term toxicities.

Disclosures

No conflicts of interest to disclose.

Contributions

OB-K and AS wrote and reviewed the editorial.

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