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COMMENTARY

Coagulopathy in CAR-T: Critical concern or mere blip?

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Despite Peng and colleagues providing an extensive review of the clinical and laboratory aspects of CAR-T-associated coagulopathy, the current literature often lacks specificity in nomenclature and gradings, and the clinical implications of coagulopathy may remain unclear. Clear recommendations on stratification and prophylaxis are still required to standardize the clinical approach to this topic.

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Bleeding, CAR-T cell therapy, Coagulopathy, Thrombosis

In this paper, Peng et al. provide a comprehensive review of the clinical and laboratory aspects of coagulopathy associated with CAR-T-cell therapy.[1] The authors revisit the concept of CAR-T-associated coagulopathy (CARAC), introduced in 2022 and not yet widely recognized in Western literature. The essential premise of CARAC is that the clinical manifestations of coagulopathy following CAR-T-cell therapy are crucial for defining the syndrome. In the original study by Mei and colleagues,[2] CARAC is described as a clinical syndrome that typically arises within the first 28 days post-CAR-T infusion, characterized by the presence of thrombosis or bleeding accompanied by thrombocytopenia and/or coagulopathy. Importantly, CARAC does not coincide with Disseminated Intravascular Coagulation (DIC) but may progress to it.

Following CAR-T cell infusion, the authors report an incidence of coagulation abnormalities ranging from 7% to 96% of cases. This wide range is evidently not useful in clinical practice and needs to be refined to identify patients truly at risk. In this paper, Peng et al. primarily focus on the clinical aspects of coagulopathy.

Bleeding: The authors summarize the incidence of bleeding, reporting it in 2%–16% of cases, predominantly as grade 1–2 events. In both literature and real-life experiences, these events are often of minor concern and are mainly attributed to transient thrombocytopenia.

Thrombosis: Venous thrombosis is reported in 2%–11% of cases, occurring more frequently as venous thromboembolism (VTE) or deep vein thrombosis (DVT). The authors note a decreasing incidence of thrombosis in lymphoma (11%) compared with myeloma (7%) and acute leukaemia (6.3%).

Interestingly, the authors discuss a study by Hashmi and colleagues[3] which reports that venous thrombosis occurring before CAR-T therapy does not increase the risk of subsequent thrombosis post-CAR-T, provided patients remain on active anti-coagulation as long as platelet counts are permissive. In line with this, another study reports a very low incidence of VTE (2.1%) in patients receiving CAR-T, with no recurrence of VTE in patients with prior episodes.[4] Although these data need further confirmation, they raise reasonable questions for countries that prohibit patients with recent thrombosis from receiving CAR-T therapy.

Disseminated Intravascular Coagulation: The authors report a varying incidence of DIC, ranging from 6% to 29%, with associated mortality in 7%–43% of cases. These patients often exhibit concomitant features of macrophage activation syndrome, high-grade cytokine release syndrome (CRS), and frequently present with extensive disease. This overlap makes it challenging to distinguish patients who die "from DIC" versus those who die "with DIC."

From a laboratory perspective, coagulopathy is variable, with alterations observed in up to 97% of cases. The severity of these alterations is crucial for guiding active intervention. Coagulopathy often presents as consumptive coagulopathy, characterized by reduced fibrinogen levels and elevated

Federica Sorà and Elena Rossi contributed equally to this study.

activated partial thromboplastin time (aPTT).[1] These alterations typically occur between days 5 and 11, coinciding with the peak of CRS. Peng and colleagues provide a comprehensive summary of current pathogenetic hypotheses regarding coagulopathy in this context, highlighting the pivotal role of inflammation-driven endothelial activation.[5,6]

Several risk factors are associated with coagulopathy following CAR-T therapy, including disease burden and CRS intensity. In summary, the greater the disease burden and CRS severity, the higher the likelihood of coagulopathy. This correlation holds true across all treated diseases, including lymphoma, lymphoblastic leukaemia, and myeloma.

Finally, an overview of current treatment approaches for coagulopathy is provided. Despite being a key focus of the article, the authors may not have deeply addressed the real amount of patients with coagulopathy that required active treatment, which appears modest in clinical practice (around 20% of patients with coagulopathy developing clinical features according to the Chinese consensus).[2]

In recent years, practical guidelines for managing coagulopathy after CAR-T therapy have been provided by various groups. Buechner and colleagues developed guidelines for paediatric and young patients with B-ALL treated with tisacel.[7] These were followed by the ASCO guidelines in 2021,[8] the Chinese guidelines,[2] and the joint EBMT/JACIE/EHA guidelines in 2022.[9]

Overall, treatment should be guided by the clinical presentation in cases of bleeding or thrombosis. Replacement therapies are encouraged if the INR or aPTT are moderately prolonged or if fibrinogen levels fall below 1.5 g/L. Specific treatments need to be supplemented by therapies aimed at resolving inflammation and macrophage activation, such as steroids or IL-6 receptor inhibitors. An interesting point concerns anti-coagulation as prophylaxis. In our opinion, adequately classified patients with hypercoagulable status may warrant primary prophylaxis, while secondary prophylaxis should be maintained as long as possible in these patients.

In conclusion, due to the wide range of manifestations, referring to "coagulopathy" after CAR-T therapy may sound overly non-specific, possibly leading to under/over-reporting of a potentially severe problem. Monitoring coagulation parameters is crucial during the first 10 days after CAR-T infusion, especially in the presence of higher-grade CRS. Active intervention is required only in selected cases. When necessary, active prophylaxis may be beneficial for high-risk patients.

Despite the revision appearing exhaustive, its limitation seems to lie in the fact that nomenclature is ambiguous and overlapping in many cited papers, where the term "coagulopathy" is employed for a wide range of phenomena, from laboratory abnormalities to CARAC, to overt DIC. This may not allow the reader to distinguish the clinical stratification of these patients. In this sense, two major clinical concerns still remain unanswered: Are some patients worthy of being excluded from CAR-T due to a recent VTE, as happens in some countries? And, secondly, in which CAR-T patients might prophylaxis be recommended?

As the weakness of current literature lies in considering all alterations of coagulation together without proper sorting for clinical impact, a wide and complete description of cases with systematic and well-classified reporting is warranted to grade coagulopathies and discriminate them from overlapping conditions such as CRS or macrophage activation syndrome.

In analogy to what was done for CRS, ICANS, and cytopenias, an expert consensus on the grading, nomenclature, and management of CAR-T-associated coagulopathies should be considered.

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