Bleeding and thrombosis in patients receiving chimeric antigen receptor T-cell therapy

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ABSTRACT

Chimeric antigen receptor (CAR) T-cell therapy has transformed the management of relapsed or refractory hematologic malignancies but is accompanied by immune-mediated toxicities that may disrupt hemostatic balance. In addition to cytokine release syndrome (CRS), immune effector cell–associated neurotoxicity syndrome (ICANS), and cytopenias, emerging data suggest an increased incidence of both thrombotic and bleeding complications following CAR T-cell infusion. We conducted a narrative review to evaluate the incidence, timing, risk factors, mechanisms, and management of CAR T-cell–associated coagulopathy, including 5 phase III randomized controlled trials and 11 observational studies published after 2020. Venous thromboembolism (VTE) was the most frequently reported thrombotic event, with rates ranging from 0.48–3.26% in trials and 2.1–10.8% in observational cohorts, typically occurring within the first 30–90 days post-infusion and often overlapping with CRS or ICANS. Arterial events were less common (<2%). Reported bleeding rates were low in trials (0–1.85%) but higher in observational studies (2.8–12.5%), frequently associated with thrombocytopenia, hypofibrinogenemia, and markers of endothelial activation. Anticoagulation for established VTE did not appear to confer excess major bleeding in limited series. Current evidence does not support routine thromboprophylaxis for all CAR T-cell recipients. Instead, thrombotic and hemorrhagic risks appear intertwined and temporally dynamic, driven by inflammation, endothelial injury, and cytopenias. Prospective studies incorporating standardized endpoint adjudication and risk stratification are needed to inform individualized prevention and management strategies.

Key words: CAR T-cell; bleeding; thrombosis; coagulopathy.

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Introduction

Immunotherapy has fundamentally reshaped the approach to hematologic malignancies by harnessing the immune system. Approaches such as immune checkpoint inhibition, monoclonal antibodies, bispecific T-cell engagers, and adoptive cellular therapies have expanded the once narrow therapeutic options for individuals with relapsed or refractory disease who previously would have had poor prognosis. Among these modalities, Chimeric antigen receptor (CAR) T-cell therapy represents one of the most transformative and promising innovations in cancer immunotherapy.[1]

CAR T-cell therapy consists of collecting the patient's own lymphocytes, most often T-cells, and genetically modifying them to express synthetic receptors that target tumor-associated antigens on the surface of cancer cells. When infused in the patient, these CAR T-cells activate and trigger a powerful cytotoxic immune response, enabling the immune system to fight cancer cells.[2,3] This strategy has led to significant improvements in outcomes for select patients with multiple myeloma and certain leukemias and lymphomas.

Since the approval of the first CAR T-cell product by the Food and Drug Administration (FDA) in 2017, significant insight has been gained regarding potential toxicities associated with this treatment modality. Characteristic adverse effects that have been well documented include cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome

(ICANS), and cytopenias.[4] These toxicities reflect profound immune dysregulation characterized by cytokine release, endothelial activation, and systemic inflammation.[5]

More recently, studies have suggested that patients receiving CAR T-cell therapy are also at an increased risk of developing coagulation abnormalities, including both hemorrhagic and thrombotic outcomes.[6-8] These events may occur across the treatment course in a patient population already pre-disposed to dysregulated hemostasis, raising the question of whether patients receiving CAR T-cell therapy are truly at increased risk of thrombotic complications beyond the risk conferred by their malignancy and other factors, and whether they are at increased risk for bleeding if subsequent anticoagulation is considered. However, there still exists a substantial knowledge gap regarding the underlying pathophysiology between CAR T-cell therapy and these adverse events. As such, evidence-based recommendations for risk stratification, prophylaxis, and management of bleeding and thrombosis in this population remain ill-defined.

In this narrative review, we aim to synthesize the current literature surrounding CAR T-cell-associated coagulopathy and unveil risk factors, incidence, timing, prognosis, management, and proposed mechanisms associated with these complications. By examining thrombosis and bleeding as closely entwined and competing risks, we also aim to clarify whether prophylactic anticoagulation may be appropriate and highlight areas in which future research can focus to further understand and mitigate the associated risks.

Methods

Data collection

We searched PubMed and ClinicalTrials.gov, with search terms such as CAR-T cell therapy AND thrombosis OR hemorrhage OR bleeding OR coagulation OR coagulopathy OR hemostasis. Two authors PLLBD and DL independently screened titles and abstracts and subsequently reviewed full texts and studies. Eligible studies included randomized controlled trials, phase II clinical trials, and retrospective or prospective cohort studies. Outcome data from clinical trials were captured from the original publication, when available – otherwise, it was collected from clinicaltrials.gov. Exclusion criteria included secondary studies, study cohort of less than 30 patients, and studies that did not include any of the specified outcomes of interest.

Results

Overview of studies

All studies were published after 2020. A total of 11 observational studies[7,9-19] and 5 randomized controlled trials[20-24] were retrieved. Observational studies focused on bleeding and thrombosis outcomes and consisted largely of retrospective chart review at the institutional level and large-scale registry-based cohorts. The randomized controlled trials were all phase 3 and were designed to assess treatment efficacy and safety, with bleeding and thrombosis captured as adverse events within a pre-defined window. For randomized controlled trials, the adverse event timeframe ranged from 28 days to 3.9 years. Among the observational studies, median follow-up time ranged from a minimum of 90 days to 40 months post-CAR T-cell infusion.

Across all RCTs and retrospective studies, adverse events were defined and graded using a range of standardized criteria. For CRS and ICANs, the most common definition was from the American Society for Transplantation and Cellular Therapy (ASTCT).[5] For general adverse events, the most common criteria were derived from the Common Terminology Criteria for Adverse Events (CTCAE), with versions varying by study.

Observational studies commonly used the modified World Health organization (WHO) criteria,[25] the International Society on Thrombosis and Hemostasis (ISTH) definitions,[26,27] or study-specific definitions for assessment of bleeding events and severity. Thrombotic events were most commonly assessed with diagnostic codes or chart review in retrospective studies.

The majority of patients in included studies were treated for diffuse large B cell lymphoma or multiple myeloma. The key study characteristics, rates of thrombocytopenia, coagulopathy (where available), thrombosis and bleeding are summarized in Table 1 for the landmark randomized controlled trials on CAR T-cell therapy and in Table 2 for cohort studies.

Thrombosis

Classification of thrombotic events

Across both randomized controlled studies and real-world cohort studies, thrombotic complications included both venous and arterial events. Of the 11 observational studies, 9 reported thrombotic events, while all 5 RCTs had at least 1 reported event. Venous thromboembolism (VTE), such as deep vein thrombosis (DVT) and pulmonary embolism (PE), appear to be the most frequently reported in both types of studies. Less frequently reported were cerebral venous sinus or splanchnic vein thrombosis. Arterial thrombotic events included ischemic strokes, transient ischemic attacks, myocardial infarctions, and peripheral arterial disease.

Timing of thrombotic events

Thrombotic events following CAR T-cell infusion seem to commonly occur within the early post-CAR T-cell period. The RCTs reported adverse events within pre-defined windows that were often limited to within 90 days after initial intervention. Despite this, thrombotic complications were noted during active treatment and early follow-up. Observational studies reported that most thrombotic events occurred within 3-4 weeks, frequently overlapping with other immune-related toxicities such as CRS and ICANS.

Incidence

Data on thrombosis, bleeding, and thrombocytopenia from the landmark RCTs in CAR T-cell therapy are summarized in Table 1. Reporting of thrombotic events across all RCTs was low with VTE rates ranging from 0.48 to 3.26%. Notably, arterial events were infrequently reported and were typically captured within serious adverse events (SAEs) in large phase II and III trials, with incidences generally below 1-2%. Similar or occasionally higher rates were noted in comparator arms. Among

observational studies, there was a wide variation in the incidence of VTE, with rates ranging from 2.1% at 30 days[14] to 10.8% at 100 days[11] which is higher than the rates reported in the clinical trials. The incidence of arterial events was lower, ranging from 0.71% at 1 year[7] to 2.4% at 1 year.[18] Notably, these studies did not include comparator groups that were not receiving CAR T-cell therapy.

Risk factors

Some studies have identified possible risk factors upon univariate analyses for thrombosis following CAR T-cell therapy. In observational cohorts, elevated D-dimer levels[7] and ICANS[7,9] were associated with venous and arterial thrombosis; CRS,[11,13] neurotoxicity,[11] and use of axicabtagene ciloleucel in non-Hodgkin lymphoma (vs tisacel in non-Hodgkin lymphoma and B-cell acute lymphoblastic leukemia)[13] were associated with VTE. Traditional risk factors such as prior history of thrombosis and central venous catheter placement appear to have inconsistent associations. Studies that assessed prior history of thrombosis did not note that prior thrombotic events conferred significant risk on development of new/recurrent thrombosis.[10,16] These findings are summarized in Table 2.

Bleeding

Classification of bleeding events

Most studies captured clinically overt hemorrhage (as SAEs). Four of the 5 RCTs reported bleeding events. Of the 11 observational studies, 7 assessed for bleeding and 6 reported at least one event. In the RCTs, reported bleeding events were predominantly mucosal or gastrointestinal, including epistaxis, hematochezia, and GI bleeding. Of note, the KaRMMa-3 trial[22] reported 2 events of fatal bleeding in the CAR T-cell arm, one intracranial and one hemothorax. Observational studies similarly described a spectrum of bleeding events, most commonly gastrointestinal bleeding, mucocutaneous bleeding, and epistaxis, with occasional reports of intracranial hemorrhage.

Timing of bleeding events

Similarly to thrombosis, bleeding events were observed in both observational studies and RCTs occur predominantly in the early post-infusion period. Observational studies demonstrated bleeding complications commonly occurring within the first 30 days after initial infusion, often overlapping with peak CRS severity, thrombocytopenia nadir, and hypofibrinogenemia.

Incidence

Among the included RCTs, the reported incidence of bleeding was low (Table 1), ranging from zero to 1.9% of aggregate numbers based primarily on SAEs in the CAR T-cell therapy arms. One study listed one non-serious adverse event that fell within the range. For perspective, the incidence of thrombocytopenia grade ≥ 3 ranged from 14.7% to 49% in CAR T-cell recipients. The incidence of bleeding was higher in the observational studies, ranging from 2.8% to 12.5% (Table 2).[10,12,15,18,28]

Table 1. Results from landmark randomized controlled trials on CAR T-cell therapy.

Study	Indication for CAR-T	Treatment	N	ATE, n (%)	VTE, n (%)	Bleeding, n (%)	Thrombocytopenia, n (%)
BELINDA[20]	R/R DLBCL	Tisa-cel	162	1 (0.62)	1 (0.62)	Serious: 3 (1.85) Non-serious: 3 (1.85)	59 (36.4)
		SoC	160	1 (0.63)	2 (1.25)	Serious: 2 (1.25) Non-serious: 10 (6.25)	79 (49.4)
ZUMA-7[21]	R/R DLBCL	Axi-cel	180	1 (0.56)	2 (1.18)	Serious: 1 (0.56) Non-serious: 0 (0)	50 (27.78)
		SoC	179	2 (1.12)	2 (1.19)	Serious: 2 (1.12) Non-serious: 0 (0)	101 (56.42)
KaRMMa-3[#22]	R/R MM	Ide-cel	254	Not reported	3 (1.18)	2 (0.79)*	136 (53.54)
		SoC	132		0 (0)	0 (0)*	36 (27.27)
CARTITUDE-4[23]	Lenalidomide-refractory MM	Cilta-cel	208	1 (0.48)	1 (0.48)	Serious: 1 (0.48) Non-serious: 6 (2.88)	113 (54.32)
		SoC	211	3 (1.42)	6 (2.84)	Serious: 2 (0.95) Non-serious: 12 (5.69)	65 (31.25)
TRANSFORM[24]	R/R DLBCL	Liso-cel	92	1 (1.09)	3 (3.26)	Serious: 1 (1.09) Non-serious: 8 (8.70)	46 (50)
		SoC	92	0 (0)	3 (3.26)	Serious: 2 (2.17) Non-serious: 6 (6.52)	62 (67.39)

*Only fatal bleeds were reported; [#]outcomes extracted from original publication. Thrombotic and bleeding events were extracted from adverse events reporting in clinicaltrials.gov unless otherwise noted. Thrombocytopenia was extracted from original publications and incidence includes all grades. Serious and non-serious adverse events were defined according to study-specific criteria. Serious events were reported separately from non-serious events, and combined numbers represented cumulative adverse events. ATE, arterial thromboembolism; DLBCL, diffuse large B-cell lymphoma; DVT, deep vein thrombosis; GI, gastrointestinal; MM, multiple myeloma; R/R, relapsed/refractory; SoC, standard of care; VTE, venous thromboembolism.

Risk factors

Few studies have attempted to identify possible factors associated with increased bleeding risk following CAR T-cell therapy. Upon multivariate analyses, factors associated with increased risk of bleeding included thrombocytopenia,[10,12,18] ICANS,[18] and CRS.[15] Wang *et al.* found that the Endothelial Activation and Stress (EASIX) score (which incorporates lactate dehydrogenase, creatinine, and platelet count)[29] and interleukin-10 were predictive of bleeding in patients undergoing CAR T-cell therapy upon multivariate analysis, with odds ratios of 7.1 and 13.8, respectively.[12] Notably, studies that specified anticoagulation therapy did not see an association between anticoagulation therapy and increased major bleeding events.[10,11,16]

Discussion

Thrombosis

Patients treated with CAR T-cell therapy are exposed to other well-known risk factors for thrombosis, including their active malignancy, hospitalization, central venous access, and lymphodepleting chemotherapy. Moreover, CAR T-cell therapy itself is hypothesized to increase the risk of thrombosis by different mechanisms, such as endothelial injury and an overall hyperinflammatory state.[30] Several studies found that thrombosis was often concurrent with other well-known CAR T-cell toxicities, such as CRS and ICANS, suggesting an overlapping pathophysiology. Moreover, it appears that patients are at the

Table 2. Results from retrospective and prospective cohort studies that reported incidence of thrombosis and/or bleeding in patients undergoing CAR T-cell therapy.

Population	Design	Sample size	Treatment	ATE, n (%)	VTE, n (%)	Bleeding, n (%)	Thrombotic risk factors[§]	Study
R/R DLBCL	Prospective	250	Axi-cel	6 (2.4)	11 (4.4)	12 (4.8)[†]	None	Ko *et al.*[18]
DLBCL, FL, and MCL	Retrospective	744	Axi-cel (n=360), tisa-cel (n=169), liso-cel (n=163), or brexu-cel (n=52)	NR	NR	13 (2.8)[‡]	NR	Rejeski *et al.*[28]
DLBCL	Retrospective	148	CD19 directed	NR	16 (10.8) at 100 days	NR	Severe CRS, neurotoxicity	Hashmi *et al.*[11]
R/R DLBCL or B-ALL	Retrospective	127	Axi-cel (n=89) or a bispecific CD 19/22 construct (n=38)	1 (0.8)	8 (6.3) at 3 months	Grade ≥ 2:12 (9.5)	Grade ≥ 3 ICANS	Johnsrud *et al.*[9,10]
DLBCL, R/R B-ALL, FL, MCL, or MM	Retrospective	140	Not specified	1 (0.7)	9 (6.4)	NR	D-dimer peak 3x ULN, ICANS	Schorr *et al.*[7]
DLBCL, TFL, MCL, PMBL or ALL	Retrospective	38	Anti-CD19	NR	1 (2.6)	0 (0)[‡]	NR	Galli *et al.*[17]
NHL or B-ALL	Retrospective	2657	Axi-cel (n=1732) or tisacel (n=925)	4 (0.15)*	34 (1.3)*	87 (3.3)	Axi-cel use	Goldman *et al.*[13]
NHL, ALL, MM, AML, Mixed acute leukemia, HL, CML	Retrospective	400	Anti-CD19 (n=237), anti-BCMA (n=77), anti-CD19 and anti-CD22 (n=45)	NR	NR	Total: 44 (11) Grade ≥ 2: 39 (9.75)	NR	Qi *et al.*[15]
NHL or B-ALL	Retrospective	56	CD19 directed	NR	NR	Total: 32.8% at 1 month Grade ≥ 2: 12.5% at 1 month	NR	Wang *et al.*[12]
NHL or MM	Retrospective	91	Anti-CD19 or anti-BCMA	0 (0)	8 (8.8)	NR	NR	Parks *et al.*[16]
CD19+ lymphomas or ALL	Retrospective	561	Axi-cel (n=332), tisa-cel (n=210), brexu-cel (n=19)	NR	6.7%	6.5%[†]	NR	Garcia *et al.*[19]
Not specified	Retrospective	97	Axi-cel	NR	2 (2.1)	NR	NR	Melody *et al.*[14]

*This study analyzed data from the FDA Adverse Event Reporting System (FAERS), and reports were only included if citing a CAR T-cell product as the primary suspect for the adverse event; [†]bleeding events defined as either major or clinically relevant non-major bleeding as per ISTH criteria; [‡]only major bleeding events were included, definition criteria not found in the original publication; [§]risk factors that were significantly associated with thrombosis (venous and/or arterial) upon univariate or multivariate analysis; bleeding events were graded based on WHO criteria unless otherwise noted. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ATE, arterial thromboembolism; CML, chronic myeloid leukemia; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma; ICANS, immune effector cell-associated neurotoxicity syndrome; MCL, mantle cell lymphoma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NR ,not reported; PMBL, primary mediastinal B-cell lymphoma; R/R, relapsed/refractory; TFL ,transformed follicular lymphoma; ULN, upper limit normal; VTE, venous thromboembolism.

highest risk of thrombosis in the early post-infusion period, which often coincides with periods of hospitalization.

Under-reporting of thrombotic events is known to be a recurring issue in cancer clinical trials,[31] and this should be considered when interpreting the included RCTs. Since most of the data on thrombosis is from observational studies that only included individuals undergoing CAR T-cell therapy and because the thrombosis rates were comparable in the treatment and control arms of the RCTs, it is still unclear whether the observed thrombotic risk can be attributed at least in part to CAR T-cell therapy. Instead, it is possible that thrombosis in these patients is mostly due to other risk factors to which they are exposed.

Bleeding

There is substantial concern for bleeding in patients receiving CAR T-cell therapy, especially due to commonly reported toxicities that disrupt hemostasis. Bleeding itself may occur as a direct consequence of treatment or malignancy and may further complicate the use of thromboprophylaxis in a patient population with a high thrombotic risk. Common CAR T-cell related adverse effects, such as thrombocytopenia and hypofibrinogenemia,[32] create a permissive environment for hemorrhagic events. Moreover, as with thrombotic events, some studies found that individuals with CRS or ICANs were more likely to have concurrent bleeding events. Bleeding therefore must be considered as a competing and potentially modifying factor in decisions on anticoagulation.

The association between bleeding and markers of endothelial activation, such as elevated EASIX scores and cytokine levels, suggests that bleeding may reflect more severe systemic inflammation rather than isolated hematologic derangements. Although uncommon, major bleeding events can occur, especially in cases of severe thrombocytopenia (grade 3-4). In the "Follow that CAR!" registry,[18] bleeding was significantly associated with worse survival upon adjusted analysis, underscoring the prognostic importance of these events.

In patients receiving anticoagulation for established thrombosis or as thromboprophylaxis, the increased bleeding risk associated with CAR T-cell therapy may frequently necessitate interruption or modification of anticoagulation. This highlights the importance of ongoing reassessment of bleeding risk balanced with thrombotic risk in an already high-risk population.

Management of anticoagulation

The available data suggest that thrombotic and bleeding complications following CAR T-cell therapy arise from overlapping pathophysiologic mechanisms, including endothelial injury, cytokine-driven inflammation, cytopenias, and coagulation factor consumption. Importantly, these complications frequently occur within the same early post-infusion window, underscoring the need for a unified management framework that accounts for both risks simultaneously rather than in isolation.

Treatment for VTE varied across studies regarding choice of anticoagulants, with most patients receiving direct oral anticoagulants (DOACs) or low molecular weight heparin (LMWH). In the 3 studies that reported anticoagulation outcomes (n=379), there was no reported bleeding or recurrent thrombosis among the 35 patients being treated for VTE with anticoagulation.[10,11,16] These data exemplify that CAR T-cell therapy does not automatically preclude anticoagulation, though additional research is needed given the small sample size. At present, there are no CAR T–specific guidelines for the prevention or management of thrombosis or bleeding. While individuals at high risk of VTE may benefit from prophylaxis, current data is lacking regarding VTE risk stratification and the clinical benefit remains undetermined. Consequently, clinical practice is largely extrapolated from general oncology and hematology principles. The bleeding and thrombosis rates discussed in this review are numerically generally comparable, mostly in the absence of anticoagulation. This means that the potential for thromboprophylaxis is likely to be limited to a subgroup of patients with low bleeding risk and high VTE risk, which remains to be identified. From the studies available, it appears that decisions surrounding thromboprophylaxis should be individualized based on patient-specific risk factors, severity of immune-related toxicities, and temporal proximity to CAR T-cell infusion.

It is also worth noting that the high incidence of thrombocytopenia in this population also poses a challenge for anticoagulation in general. Therefore, it is important to adapt anticoagulation in the individual patient based on the indication (e.g., thromboprophylaxis *vs* acute VTE), while considering thrombocytopenia and other bleeding risk factors, which are often dynamic. Accordingly, LMWH is usually preferred over DOACs when anticoagulation is used in the initial period (e.g. first 30 days) after CAR T-cell infusion when thrombocytopenia is more prevalent. Recent studies have attempted to develop novel grading systems in place of the HEMATOTOX grading system to better standardize thrombocytopenia that can occur after CAR T-cell therapy, including a variant of the immune effector cell-associated hematotoxicity (ICAHT) score, the T-ICAHT score.[28] In this multicenter observational study, it was observed that an early platelet nadir was noted around day 5 associated with lymphodepletion, with a second nadir occurring around day 30 at time of infusion. The level and rate of platelet recovery appeared to be associated with T-ICAHT scoring. Overall, T-ICAHT grades were also associated with increased transfusion burden and bleeding events and inversely associated with overall survival. In considering thromboprophylaxis, these scores may play an important role in identifying patients susceptible to severe thrombocytopenia and therefore drive individual anticoagulation decisions. This score may also inform monitoring of platelet counts to allow for potential dose adjustment of anticoagulation across all indications.

Hypofibrinogenemia

Patients receiving CAR T-cell therapy are also at risk of developing hypofibrinogenemia, particularly during the early post-infusion period and decreased fibrinogen levels appear to be associated with development of higher-grade CRS. In observational cohorts, median fibrinogen nadirs ranged from 227-307mg/dL, with reported minimum values as low as 50-66 mg/dL.[7,10] Some studies associated CRS ≥2 with grade 3-4 hypofibrinogenemia in up to 69% of patients,[33] mostly within the first 30 days following CAR T-cell infusion.

The decreased fibrinogen levels are likely to be multifactorial. Etiologies include consumptive processes, decreased he-

patic synthesis in the setting of critical illness or hepatic dysfunction, dilution effects from transfusion or resuscitation, or medication related effects.[34-37] In addition, immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome, an increasingly recognized CAR T-cell-related toxicity characterized by hyperinflammation, macrophage activation, hypofibrinogenemia, hyperferritinemia, and cytopenias,[38] can further add to the multiple conditions contributing to low fibrinogen levels in this population.

Disseminated intravascular coagulation (DIC) is a consumptive process resulting in low fibrinogen levels in this context,[7,9,17] likely occurring due to inflammation and endothelial activation arising from therapy and severe CRS.[6,17] DIC severity can vary from strict laboratory abnormalities to life-threatening thrombosis or bleeding.[39] However, the prognostic importance of DIC in patients receiving CAR T-cell therapy is unclear, with studies reporting inconsistent associations with bleeding, thrombosis, and progression-free or overall survival.[7,9,17] Most studies describe isolated laboratory abnormalities such as low fibrinogen levels, elevated D-dimer, prolonged prothrombin time, or thrombocytopenia, rather than the composite of DIC-related abnormalities. This could be partly attributed to the fact that conventional scoring algorithms, such as the ISTH DIC score, may be confounded by co-occurring abnormalities in this population (e.g., thrombocytopenia due to bone marrow suppression, and hypofibrinogenemia due to tocilizumab administration).[40] When taken together, the data suggest that while hypofibrinogenemia can be considered to be an adverse event following CAR T-cell therapy, further classification is needed in order to determine the prevalence of DIC itself post infusion. Rather, low fibrinogen likely reflects the spectrum of inflammation and endothelial disturbances as a whole and must be evaluated carefully when taking into account further bleeding and thrombotic risk.

Limitations

Reporting of thrombotic and bleeding outcomes are not consistent across studies. For the RCTs, thrombosis or bleeding were not a prespecified endpoint. For instance, in some studies, it was not clear whether bleeding events did not occur or were not reported due to not being serious events.[21] Non-serious thrombotic events, catheter-associated thromboses, and asymptomatic VTE were unlikely to be captured, which could explain the low incidence of thrombotic events in RCTs compared to observational studies. Additionally, comparator arms often involved intensive chemotherapy and autologous stem cell transplantation, which independently confer substantial thrombotic and bleeding risk, further complicating direct comparisons.

Observational studies were often underpowered to perform extensive multivariate analyses; therefore, it is likely that there are other important risk factors for thrombosis and bleeding that did not meet statistical significance. For bleeding specifically, it is also notable that some observational studies employed standardized bleeding definitions, such as modified World Health Organization (WHO) criteria which can include both ISTH-defined major and clinically relevant non-major bleeding events, likely contributing to higher reported incidence compared with RCTs.

Conclusions

CAR T-cell therapy remains at the forefront burgeoning treatment for hematologic malignancies. As with other immunotherapy, it is accompanied by risk factors that must be carefully weighed when determining whether to pursue treatment. In addition to immune system dysregulation, complex disturbances in hemostasis that manifest as both thrombotic and bleeding complications highlight the careful balance that needs to be met when anticipating and treating adverse events. The association between thrombosis and bleeding and additional toxicities such as CRS/ICANs suggests overlapping mechanisms, further emphasizing complexity and interconnectedness of the underlying physiology of patients with malignancy.

Thrombotic and bleeding events were likely underreported in clinical trials, highlighting the importance of standardizing the adjudication of these endpoints and integrating them with toxicity grading frameworks. While underreported, thrombotic events are clinically relevant and bleeding risk, driven by thrombocytopenia, hypofibrinogenemia, and immune-mediated toxicities, remains a critical counterbalance, particularly when considering anticoagulation. The available data noted in this review do not support routine thromboprophylaxis for all CAR T-cell recipients but instead underscore the need for individualized risk stratification.

Future studies should focus on evaluating risk-adapted strategies to prevent thrombosis and bleeding in patients receiving CAR T-cell therapy. Incorporation of biomarkers of endothelial activation and inflammation may further refine patient selection, but this remains to be studied. Data on thrombosis rates in specific higher risk populations, such as those with CRS or ICANS, could inform the need for research on risk stratification and thromboprophylaxis in these patients. Ultimately, optimizing thrombosis and bleeding outcomes in CAR T-cell therapy will require an integrated approach that acknowledges the dynamic interplay between thrombosis and bleeding, with management strategies tailored to maximize benefit while minimizing harm.

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