Update on Thrombosis Risk in Patients with Cancer: Focus on Novel Anticancer Immunotherapies

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Abstract

Thromboembolic complications, including venous thromboembolism (VTE) and arterial thromboembolism (ATE), increase mortality and morbidity, and delay treatment in patients with cancer. Therefore, an increased understanding of underlying risk profiles, the identification of risk factors and predictive biomarkers, and ultimately the development of specific cardiovascular prevention strategies in patients with cancer is needed. Medical anticancer therapies have undergone a remarkable development in recent years with the advent of targeted and immunotherapeutic treatment options, including immune checkpoint inhibitors (ICI), chimeric antigen receptor (CAR) T-cell therapies and T-cell engaging bispecific antibodies (BiTEs). These developments have important implications for the accompanied risk of thromboembolic events in patients with cancer. First, the increased use of these highly effective therapies renders a growing proportion of patients with cancer at risk of thromboembolic events for a prolonged risk period due to an increase in patient survival despite advanced cancer stages. Second, potential direct cardiovascular toxicity and prothrombotic effect of novel anticancer immunotherapies are a matter of ongoing debate, with emerging reports suggesting a relevant risk of VTE and ATE associated with ICI, and relevant dysregulations of hemostasis in the frequently observed cytokine-release syndrome associated with BiTEs and CAR T-cell therapy. The aim of the present narrative review is to summarize the implications of the emerging use of anticancer immunotherapy for thromboembolic events in patients with cancer, and to provide an overview of available data on the rates and risk factors for VTE and ATE associated with ICI, CAR T-cell therapy, and BiTEs.

Keywords

- cancer
- venous thrombosis
- arterial thrombosis
- immunotherapy

Introduction: Cancer and Thromboembolic Risk

Patients with cancer face an increased risk of thromboembolic and atherothrombotic complications.[1] These include venous thromboembolism (VTE), comprising deep vein thrombosis and pulmonary embolism, with a ninefold increased VTE risk after cancer diagnosis compared with the general population, and arterial thromboembolic events (ATE), comprising myocardial infarction, ischemic stroke, and acute peripheral arterial occlusion, which is increased twofold in cancer patients compared with the noncancer

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population.[2,3] The increased risk of cardiovascular events reflects a complex and multifactorial underlying pathophysiology.[1,4] First, patient-specific factors including demographics, comorbidities, and genetic predisposition, including prothrombotic mutations or blood type, affect the risk of cancer-associated thromboembolic events.[4–6] Further, most prominently, risk profiles for VTE and ATE largely depend on cancer-specific prothrombotic risk factors including cancer type, stage, and biology, with a known association between hypercoagulability and more aggressive clinical behavior of cancers.[2,7] Finally, the risk of cancer-associated thromboembolic events is affected by iatrogenic factors including cancer surgery, radiotherapy, and medical anticancer therapies.[5,8] Of these, certain chemotherapy agents have been linked to an increased cardiovascular risk.[8] Besides these, nonchemotherapeutic systemic treatments, including hormonal therapies such as tamoxifen or antiangiogenic therapies, also affect the prothrombotic risk of treated patients.[9]

In recent years, a growing population of cancer patients qualifies for treatment with targeted or immunotherapeutic agents. Currently, availability and quality of data reporting the underlying risk of VTE and ATE of these novel agents is highly heterogenous. Further, for very recent advances in medical oncology and hemato-oncology, including the advent of cell-based immunotherapy, the impact on cardiovascular risk is still not well described. The aim of the present narrative review is to discuss the prevalence and risk factors for VTE and ATE associated with novel immunotherapeutic treatments in patients with cancer in general and summarize specifically the available data for selected novel agent groups such as immune checkpoint inhibitors (ICI), chimeric antigen receptor (CAR) T-cell therapy, and bispecific T-cell engaging therapies (BiTEs).

Emerging Role of Novel Anticancer Therapies

Medical oncology and hemato-oncology have been undergoing a continuous development toward biomarker-driven, targeted, and immunotherapeutic personalized treatments.[10,11] Consequently, unprecedented treatment response patterns and survival times are achieved in certain subgroups of treated patients, oftentimes despite advanced cancer stages and treatment settings.[10–12] Further, novel therapies are increasingly used in curative treatment intents in the adjuvant and even neoadjuvant setting. These developments lead to a growing population of cancer survivors and patients living with active cancer under continuous disease control.[12] These changes are largely based on advances in the field of cancer immunotherapy, with the increasing use of ICI and the development of cell-based immunotherapies including CAR T-cell therapy and BiTEs.

Importantly, currently available data on risk factors, biomarkers, and risk prediction models specifically for cancer-associated VTE are based on the era of "traditional" chemotherapy-based treatments, which no longer reflect the variety of systemic treatment approaches used in clinical practice. The current changes in the treatment landscape have a potentially large impact on the underlying cardiovascular risk patterns and have not been systematically and sufficiently addressed to date. Furthermore, potential direct prothrombotic effect and specific cardiotoxicities/cardiovascular toxicities of emerging anticancer therapies are a matter of ongoing debate, with emerging data suggesting important clinical implications for the risk of cancer-associated thromboembolic events of novel treatment modalities. For example, a Danish nation-wide cohort study reported an overall risk of developing VTE of 1.7% within 6 months after cancer diagnosis.[2] Stratified according to the type of systemic therapy within 4 months after cancer diagnosis, risk was lowest in patients receiving no systemic therapy (1.1%) or hormonal therapy only (0.9%), elevated with chemotherapy (3.5%), and was highest in patients undergoing targeted therapy (4.2%), with a corresponding risk of protein kinase inhibitors, vascular endothelial growth factor (VEGF) targeted therapies, and ICI of 5.9, 6.1, and 4.1%, respectively.[2] These data do not allow the inference of a causal prothrombotic risk of the individual agent groups, yet underline the potentially emerging populations at high risk of thromboembolic events among cancer patients.

Importantly, selected targeted anticancer therapies such as antiangiogenic agents have been established as systemic treatments for a variety of cancers for over a decade. For these, broad data are available to inform treating physicians on the associated cardiovascular risk profiles. For example, for the anti-VEGF monoclonal antibody bevacizumab, concurring preclinical data and large-scale data from clinical cohorts and randomized controlled trials (RCTs) suggest a causal prothrombotic effect.[9,13,14] Similarly, tyrosine kinase inhibitors (TKIs) targeting the VEGF receptor have been repeatedly linked to an increased risk of ATE.[9,15]

In contrast, for emerging immunotherapies including ICI, there is lack of data on specific cardiovascular adverse events including VTE and ATE from clinical trials, and discrepant observations from clinical real-world cohort studies have been reported.[16] For other very recently developed treatments such as CAR T-cell therapies and BiTEs, the data on their impact and individual risk profiles of thromboembolic events are scarce. In the following sections, the specific clinical background and a summary of data on cardiovascular adverse events of these novel anticancer treatments are provided.

Immune Checkpoint Inhibitors

The development of ICI marks the advent of a new era of cancer immunotherapy. With the targeted blockade of immunosuppressive pathways ("immune checkpoints") overexpressed by cancer cells, physiologic T-cell-mediated anticancer immune effects are restored. Currently, ICI are increasingly used in the treatment of a variety of cancer types including melanoma, lung cancer, urogenital cancers, and various others. Recent estimates indicate that 44% of cancer patients are eligible for ICI treatment, with continuously emerging treatment indications expanding to the adjuvant and neoadjuvant treatment

settings.[11] Importantly, the reinvigoration of antitumoral immunity leads to a strong systemic inflammatory stimulus in treated patients, characterized by a variety of immune-mediated adverse events.[17] Systemic inflammatory pathways are tightly linked to the hemostatic system. Accordingly, autoimmune diseases with a similar clinical phenotype such as ICI-associated immune-related adverse events have an increased risk of thromboembolic complications compared with the general population.[18–21]

In the large-scale clinical trials evaluating ICI efficacy, thromboembolic events were inconsistently reported or the rates were generally low, with a pooled VTE risk of only 2.7% and ATE risk of 1.1% in an early meta-analysis.[22] Further, in a large-scale meta-analysis including 29,592 patients, comparing cardiovascular events from 48 RCTs between the ICI arm and the respective control arm, an increased risk of myocardial infarction and ischemic stroke was observed with ICI, whereas the risk of VTE was similar between the treatment arms.[23] However, the reported risks in the respective ICI arms were low, contrasting the anticipated moderate to high risk of thromboembolic events of treated patients based on the type and stage of cancers.[22,23] Therefore, these comparative data need to be interpreted with caution.[24]

Similarly, data from clinical practice cohorts emerged, reporting a substantial risk of both VTE and ATE during ICI therapy (►Table 1), suggesting a potential underreporting of cardiovascular events in landmark clinical trials of ICI.[24,25] In a single-center retrospective cohort study, including 672 patients with different cancers treated with ICI, followed for a median of 8.5 months, the cumulative incidence of VTE and ATE was 12.9 and 1.8%, respectively, with homogenously high VTE risk observed between different cancer types.[26] Similarly, a multicenter cohort study including 522 patients with metastatic cancer treated with ICI reported a risk of 10.5% for VTE and 1.3% for ATE.[27] In the largest clinical dataset published to date, Roopkumar et al reported a cumulative risk of VTE of 24% in 1,686 patients with different cancers treated at a single institution.[28] Further, several studies reported the risk of thromboembolic events with ICI therapy in selected cancer types, with a homogenously high cumulative risks in cohorts of patients treated with non-small-cell lung cancer (NSCLC; VTE: 9.9% and ATE: 1.3%), melanoma (VTE: 12.9% and ATE: 4.5%), and urothelial cancer (VTE: 13% and ATE: 2%).[29–31]

Besides thromboembolic events, the impact of ICI therapy on atherosclerotic events has been studied recently. In a large-scale single-center cohort study involving 2,842 patients treated with ICI, risk of cardiovascular events including a composite of myocardial infarction, ischemic stroke, and coronary revascularization was increased threefold compared with a matched population of non-ICI-treated patients.[32] Similarly, in a case-crossover analysis, the risk of cardiovascular events was increased from 1.37/100 patient-years (PY) before the start of ICI to 6.55/100 PY after ICI initiation.[32] Interestingly, in an imaging substudy of this cohort including 40 patients, the rate of atherosclerotic plaque progression increased more than threefold after the initiation of ICI therapy.[32]

However, a causal prothrombotic and proatherogenic effect of ICI is still unclear, based on the potential risk of bias and conflicting data from comparative analyses from clinical cohort studies. For example, Gong et al[65] reported an increased risk of VTE associated with ICI therapy in a case-crossover design, with rates of 4.9/100 PY before and 8.9/100 PY after ICI initiation, translating to an incidence rate ratio of 1.84 (95% confidence interval [CI]: 1.54–2.19) for ICI therapy. Further, comparative data in a matched analysis from a nationwide cohort study suggest an increased risk of VTE with ICI therapy for the investigated subgroups of patients with lung cancer and melanoma.[33] In a very recent retrospective cohort study, comparing crude VTE rates in patients with advanced NSCLC ($n = 508$), a higher risk was observed for ICI (23.5%) compared with chemotherapy (13.8%).[34] In contrast, a recent study reporting the cumulative risk of VTE in patients with advanced NSCLC undergoing systemic therapy ($n = 2{,}299$) described a similarly high risk of VTE between patients treated with chemotherapy, ICI, and combined therapy of chemotherapy and ICI, with corresponding incidence rates of 13.5/100 PY, 18.0/100 PY, and 22.4/100 PY, respectively.[35] Further, in a recent health care database analysis including 1,823 patients with advanced cancers, a similarly high risk of VTE was observed with ICI therapy compared with patients treated with chemotherapy (6-month cumulative risk: 8.5 vs. 8.4%), with no significant differences in propensity score weighted analysis (weighted hazard ratio: 1.06; 95% CI: 0.88–1.26).[36]

Complementary to these clinical cohort data, recent reports of experimental studies suggest a potential pathophysiologic link between ICI-induced systemic inflammation and hypercoagulability. First, enhanced clot formation was observed in tumor-bearing mice with ICI treatment.[37] Further, ICI treatment resulted in increased tissue factor (TF) expression of tumors in a mouse model, with corresponding elevated levels of TF-bearing extracellular vesicles in the murine circulation. TF overexpression was observed for both cancer cells and cells of the tumoral microenvironment including monocytes, neutrophils, and stromal cells, consequently translating to larger thrombi observed in ICI-treated mice.[38] Similarly, an increased formation of prothrombotic neutrophil extracellular traps (NETs) was observed with ICI treatment in another murine model, with corresponding higher rates of neutrophil–platelet aggregates and a higher percentage of neutrophils in thrombi of ICI-treated mice, suggesting immunothrombosis as potential underlying pathophysiologic contributor to ICI-associated hypercoagulability.[39] Finally, preclinical studies suggest a causal relationship between ICI and accelerated atherosclerosis via various proinflammatory pathways.[40] Synoptically, immune checkpoints including PD-1 suppress T-cell-mediated plaque inflammation and progression, which results in enhanced atherosclerosis with immune checkpoint blockade.[40]

Irrespective of potential underlying causality, the high absolute risk of VTE and ATE observed during ICI therapy warrant a thorough characterization of risk patterns and exploration of risk prediction models to select patients who might benefit from primary cardiovascular prophylaxis

Table 1 Selected cohort studies on risk of thromboembolic events in ICI-therapy

Design	*n*	Setting	Median follow-up (mo)	VTE	ATE	Risk factors
Single-center cohort study[26]	672	Different cancer types (30% melanoma, 24% NSCLC)	8.5	12.9% CI 5.0% CI (6 mo) 7.0% CI (12 mo)	1.8% CI	Prior VTE, Stage IV Khorana score: negative
Multicenter cohort study[27]	552	Stage IV, different cancers (47% NSCLC, 32% GU, 17% melanoma)	12.1	10.5% on ICI	1.3% on ICI	AC at baseline Khorana score: negative
Single-center cohort study[28]	1,686	Different cancer types (13% melanoma, 50% NSCLC)	14.4	24% 7.1% (6 mo) 10.9% (12 mo)	n.r.	Younger age, metastasis, biomarkers
Health care database analysis[36]	1,823	Different cancers, first line (stages III, IV)	–	8.5%	n.r.	–
Single-center cohort study[35]	2,299 (ICI: $n=605$; CTX: $n=1,092$; ICI + CTX: $n=602$)	Advanced NSCLC, first line	9.1	ICI: 17.8/100PY 13.4% (overall) ICI + CTX: 22.4/100PY 18.1% (overall)	–	–
Single-center cohort study[29]	279	Urothelial cancer	5.6	13%	2%	–
Single-center cohort study[30]	228	Melanoma	27.3	8.0% CI (6 mo) 12.9% CI (12 mo) $n=37$ events	2.2% CI (6mo) 4.5% CI (12mo)	ICI combination Khorana score ≥ 1 Prior CAD
Single-center cohort study[43]	176	NSCLC	6.1	4.5% CI (6 mo)	n.r.	AC at baseline Khorana score: negative
Single-center cohort study[31]	593	NSCLC	12.7	9.9%	1.3%	Younger age, higher PDL1, smoking
Post hoc analysis of multicenter retrospective cohort study[64]	748	Advanced NSCLC, PDL1 $\geq 50\%$, pembrolizumab monotherapy	25.8	14.8%	n.r.	–

Abbreviations: AC, anticoagulation; ATE, arterial thromboembolic events; CAD, coronary artery disease; CI, cumulative incidence; CTX, chemotherapy; GU, genitourinary; ICI, immune checkpoint inhibitor; n.r., not reported; NSCLC, non-small-cell lung cancer; PDL1, programmed death ligand 1 expression; PY, patient years; VTE, venous thromboembolism.

strategies. Further, the potential impact of ICI toward hypercoagulability and atherosclerosis has crucial implication for the long-term safety profiles, especially regarding the increasing use of ICI in curative treatment intents. Data on clinical risk factors specifically for ICI-associated VTE remain inconclusive. Importantly, known prothrombotic risk factors for cancer-associated VTE in the general oncologic population such as the underlying type of cancer did not stratify VTE risk in ICI therapy.[9,25,26] The Khorana score is currently suggested to be used as risk stratification tool to select ambulatory patients with cancer for primary thromboprophylaxis.[41] Importantly, this score was developed in the pre-ICI era, with the original derivation cohort including chemotherapy-treated patients only.[42] Conflicting data were reported on the predictive utility of the Khorana score in ICI-treated patients,[9,25] with multiple studies suggesting the absence of VTE risk stratification in this setting.[26,27,43,44] Beyond clinical risk factors, little data are available regarding biomarker-based VTE risk prediction in ICI therapy. In a small exploratory subanalysis ($n=25$) of a single-center cohort study ($n=1,686$), elevated pretreatment levels of inflammatory biomarkers including myeloid-derived suppressor cells, interleukin 8, and soluble vascular cell adhesion protein 1 were present in patients developing VTE under ICI compared with those without VTE, suggesting a potential impact of an inherently higher inflammatory threshold for subsequent risk of ICI-associated thrombotic events.[28] Further, a recent analysis from a retrospective cohort study ($n=405$) suggests an early increase of the inflammatory acute phase C-reactive protein after ICI initiation as a biomarker for an increased VTE risk.[45]

Synoptically, high rates of VTE (8–25%) and ATE (2–5%) were observed in clinical cohorts of patients with cancer

treated with ICI. To date, a causal prothrombotic effect of ICI is unclear, with conflicting data from available comparative studies. However, emerging preclinical evidence link ICI-induced inflammation with hypercoagulability and atherosclerosis. Further, the prolonged survival of treated patients and the substantial observed thrombotic risk warrant specific evaluations of cardiovascular safety and the development of individualized cardiovascular prediction and prevention strategies during ICI therapy.

CAR T-Cell Therapy

Adoptive cell-based immunotherapy has made significant progress over the recent years with the development of genetically modified T cells of patients, utilizing a CAR, which links the antigen detection property of an antibody domain with the T-cell activating properties of a T-cell receptor.[46] CAR T-cells are currently used effectively in the treatment of relapsed or refractory B-cell malignancies including diffuse large B-cell lymphoma, acute lymphoblastic leukemia (ALL), and multiple myeloma.[46] Currently, numerous different CAR T-cell-based therapies are in development or undergoing clinical testing in a variety of hematologic and solid cancers.[47] Importantly, upon application of CAR T cells, the anticancer effect is frequently accompanied by a strong systemic inflammatory stimulus, which can prompt a cytokine release syndrome (CRS).[48] Clinically, CRS presents mostly with fewer and hypotension, with severe cases characterized by rapid clinical deterioration, shock, and high mortality.[49] Importantly, hemostatic dysregulations are frequently observed in CRS, including prolonged coagulation times, elevation of D-dimer, low fibrinogen, and reported cases of disseminated intravascular coagulation (DIC).[48] Clinically, thromboembolic and hemorrhagic complications have recently been reported as adverse events in association with CRS (►Table 2). In a large multicenter retrospective analysis involving 1,305 patients treated with CAR T-cell therapy, 454 (34.7%) developed CRS. Of those, within 2 weeks after therapy, 7.6% developed VTE, 3.1% had myocardial infraction or ischemic strokes, and 2.8% were diagnosed with DIC. Further, 3.1% of patients with CRS developed pulmonary or gastrointestinal bleeding and 8.0% had a diagnosis of an indeterminate bleeding event.[50] Similarly, another retrospective cohort study including 130 adult patients undergoing CD-19-targeted CAR T-cell therapy reported an absolute risk of bleeding events of 9.4% and for thrombotic complications of 6.3% within 3 months after treatment.[51] Finally, a retrospective cohort study reported the risk of VTE in cohorts of patients with B-cell lymphoma ($n = 37$) and myeloma ($n = 54$). The corresponding absolute risk of VTE over 60 days after CAR T-cell infusion was 11 and 7%, respectively, with a median time to onset of VTE of 20 days (range: 6–39 days).[52] These data suggest thromboembolic events as potential clinical manifestations of CRS in CAR T-cell-treated patients, again underlining the important pathophysiologic implications of antitumoral immunotherapy for systemic hemostatic dysregulation. Further, bleeding events emerged as important complications associated with CAR T-cell therapy. In part, the observed hemorrhagic risk might be explained by acute hemostatic dysregulations in the setting of CRS. However, as patients with hematopoietic malignancies undergo lymphodepleting chemotherapy prior to CAR T-cell infusion, chemotherapy-induced thrombocytopenia is common in treated patients, and long-term thrombocytopenia is a frequent complication in CAR T-cell therapy, which might explain the high bleeding rates after therapy (►Table 2).[53] Therefore, the development and implementation of thromboprophylaxis strategies specifically in CAR T-cell therapy is complicated by the complex underlying toxicity profiles and concurrently elevated thrombotic and bleeding risks, potentially hampering the risk-to-benefit ratio of thromboprophylaxis in this setting.

Bispecific T-Cell Engaging Antibodies

Very recently, BiTEs were developed as another type of T-cell-based cancer immunotherapy, using bispecific antibodies to link cytotoxic T cells to cancer cell surface epitopes and thereby induce anticancer immunity.[54] Beyond the original use of the BiTE blinatumomab in B-ALL, several additional BiTEs are currently undergoing clinical testing in various hematologic and solid cancers.[54] Further, tebentafusp has recently been introduced in clinical practice for the treatment of a subclass of patients with uveal melanoma.[55] Similar to CAR T-cell therapy, the induction of antitumor cytotoxic T cells can result in CRS as an adverse event.[54] However, as opposed to CAR T cells, BiTEs are usually repeatedly used over the treatment time frame, which also affects the inflammatory adverse event profile of treated patients. To date, very limited data are available on hemostatic dysregulations associated with CRS with BiTEs. One retrospective cohort study including 36 patients with ALL treated with blinatumomab demonstrated indications for a strong transient hemostatic activation after treatment initiation, characterized by elevated peak D-dimer levels especially after the first treatment cycle.[56] Further, sparse data exist on clinical manifestations of hemostatic complications during BiTEs, with currently no data available on risk of VTE and/or ATE. In a multicenter phase II clinical trial evaluating blinatumomab in B-ALL ($n = 189$), four patients developed DIC (2%). In addition, two patients suffered a fatal hemorrhagic event during the treatment period.[57]

Beyond BiTEs, different bispecific antibodies are currently in development and undergoing clinical testing.[58] The bispecific antibody amivantamab was demonstrated to markedly improve outcomes of patients with epidermal growth factor receptor (EGFR) mutated NSCLC in combination with the TKI lazertinib.[59,60] Interestingly, in a large RCT including patients with advanced NSCLC in the first-line setting, VTE occurred in 37% of patients treated with amivantamab + lazertinib ($n = 429$) compared with 9% in the osimertinib control arm ($n = 429$).[60,61] Accordingly, in another RCT of patients with advanced EGFR-mutated NSCLC after progression to osimertinib, the reported risk of VTE in patients treated with amivantamab + lazertinib in addition to chemotherapy ($n = 263$) was 22%, compared with 5% in the

Table 2 Risk of thromboembolic and bleeding events with CAR T-cell therapy

Study type	Population	Study specifics (sample size, follow-up)	VTE	ATE	Bleeding/ DIC	Risk factors and timing of onset
Retrospective multicenter health care database analysis[50]	Patients receiving FDA-approved CAR-T who developed CRS	$N = 1{,}305$ patients with CAR-T, $n = 454$ CRS (34.7%) Follow-up: 2 wk after CRS	7.6% DVT/PE	3.1% MI or stroke	2.8% DIC, 3.1% lung/GI bleed, 8.0% unspecified bleeding	n.r.
Single-center retrospective cohort study	Adult patients; LNCL, B-ALL Axi-cel or CD19/ CD22-bispec.-CAR	$N = 127$ Follow-up: 3 mo after CAR-T Bleeding and thrombosis ≥ 2°CTCAE	6.3%[a]	n.r.[a]	9.4% bleeding	Bleeding: median 18 d (range 8–30) VTE: median 29 d (range: 2–91) Risk factors for bleeding: higher age, lower baseline platelets, lower nadir platelets and fibrinogen, and higher LDH; ICANS associated with bleeding and thrombosis
Single-center retrospective cohort study	CAR-T for R/R NHL or MM	$N = 91$ (37 NHL, 54 MM) Follow-up: 60 d after CAR-T	8.8% (11% NHL, 7% MM)	0%	n.r.	Mean time to VTE: 20 d (range: 6–39)
Multicenter, retrospective cohort study	Adult patients, CAR-T for R/R NHL or MM	$N = 140$ (106 NHL, 34 MM) Thrombotic events ≥ 2° CTCAE Follow-up: 30 d after CAR-T[b]	6.4%	0.7%	n.r.	Median time to onset of thrombotic event: 23.5 d Risk factors: peak D-dimer, ICANS grade
Single-center retrospective cohort study	CD19 CAR T-cell therapy for LBCL	$N = 148$ Follow-up: 100 d after CAR-T	11%	n.r.	n.r.	n.r.

Abbreviations: axi-cel, axicabtagene ciloleucel; B-ALL, B-cell acute lymphoblastic leukemia; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; CTCAE, common terminology criteria for adverse events; DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis; GI, gastrointestinal; ICANS, immune effector cell associated neurotoxicity syndrome; LBCL, large B-cell lymphoma; LDH, lactate dehydrogenase; MI, myocardial infarction; MM, multiple myeloma; n.r., not reported; PE, pulmonary embolism; R/R NHL, relapsed/refractory B-cell non-Hodgkin's lymphoma.

Note: Risk represents crude percentages, unless otherwise specified.

[a]Thrombotic events included deep venous thrombosis ($n = 5$), thrombotic stroke ($n = 1$), and splanchnic vein thrombosis ($n = 2$).

[b]Follow-up: 30-day hospitalization period post-CAR T-cell infusion and continued in patients with later complications.

chemotherapy control arm ($n = 243$).[59] These findings again emphasize the potential large implications of anticancer therapies with novel mechanism of action toward risk of cancer-associated thrombosis.

Discussion

With the advent of modern immunotherapy, remarkable improvements in treatment responses and patient survival have been achieved, revolutionizing treatment of patients with different cancers. However, these developments are accompanied by challenges including their impact on cancer-associated thrombosis.

First, a subgroup of patients with cancer treated with cancer immunotherapy achieves ongoing treatment response, resulting in improvement of survival, even despite advanced cancer stages. This newly emerging population of patients living longer with active, stable malignancies poses novel challenges in the interdisciplinary care of cancer patients. Importantly, the longer time at risk of thromboembolic events, in combination with the seemingly constant increase in risk of VTE and ATE during continuous cancer immunotherapy, changes the general risk pattern of thromboembolic events in patients with cancer.[26,28] Second, the decrease in cancer-specific mortality observed with cancer immunotherapy paradoxically increases the clinical

relevance of thromboembolic events as secondary contributors to morbidity and mortality. Especially given the long-term benefit and increasing use in curative treatment settings, specific long-term safety evaluations of thromboembolic and atherothrombotic events are urgently needed. Third, the observed high rates of thromboembolic events particularly with ICI have important clinical and scientific implications. Currently, a direct prothrombotic effect of ICI is unclear, and future research is needed to elucidate potential pathophysiologic pathways that might link ICI-induced systemic inflammation with hypercoagulability. However, irrespective of potential causality, the observed substantial thromboembolic risk associated with cancer immunotherapies requires research to identify risk factors, biomarkers, and specific risk prediction models to enable future personalized cardiovascular prediction and prevention strategies. Fourth, the current challenges and unclarity regarding thromboembolic risk profiles of patients treated with cancer immunotherapies, especially considering the discrepant data from clinical trials compared with real-world cohorts, highlight the general issue in medical oncology, with an insufficient focus on cardiovascular adverse events of novel anticancer therapies. Interestingly, a lower risk of VTE has previously been reported in chemotherapy trials as opposed to thromboprophylaxis trials and real-world data in pancreatic cancer, suggesting low awareness resulting in underreporting of thromboembolic events as secondary outcome events.[62,63] Further, clinical trials evaluating immunotherapy frequently apply a reporting and severity threshold for adverse events, which do not allow general post hoc analyses of respective thromboembolic risk.[24] In the future, more focus should be placed on a precise characterization of cardiovascular adverse events of novel anticancer treatment approaches. Finally, established risk prediction models for thromboembolic events in ambulatory patients with cancer have been reported to underperform in the setting of cancer immunotherapy. For example, discrepant data exist on the predictive utility of the Khorana score in patients with ICI, with several large validation cohorts suggesting no appropriate VTE risk stratification.[26,27,43,44] This underlines the necessity to critically validate existing risk models developed in the pre-immunotherapy era in patient cohort treated with novel anticancer immunotherapy prior to uncritically applying them. Further, the development of specific thromboprophylaxis strategies in the setting of CAR T-cell therapy must consider the underlying bleeding risk and frequency of short- and long-term thrombocytopenia in treated patients. Synoptically, continued scientific efforts are needed to develop novel and cancer- and treatment-type specific risk prediction models for thromboembolic events.

Conclusion

Immunotherapeutic approaches are constantly changing the treatment landscape of patients with cancer. The impact on risk of thrombosis is a matter of ongoing debate. High rates of thromboembolic events were reported in real-world cohort studies and registries of patients treated with ICI, yet a causal prothrombotic effect has not been established. Furthermore, severe hemostatic dysregulation has been observed with adoptive cellular immunotherapy-associated CRS. Future research should focus on identifying putative prothrombotic pathways of cancer immunotherapy and developing specific cardiovascular prediction and prevention strategies in a newly emerging population of patients with cancer.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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