Thrombosis and Immune Checkpoint Inhibitors

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Thromboembolism is a common complication in patients with cancer and is associated with significant morbidity and mortality. Anticancer treatment is a known risk factor of cancer-associated thrombosis. Immune checkpoint inhibitors have become a mainstay of treatment in various cancers. Both venous and arterial thrombosis have been increasingly reported as adverse events associated with immune checkpoint inhibitors in recent studies, with a cumulative incidence of venous thrombosis to be 5–8% at 6 months and over 10% at 12 months. Additionally, rates of approximately 1–5% for arterial thrombosis were reported at 12 months. Data also showed an association of thromboembolism with adverse survival. Many pertinent clinical questions in this population deserve further investigation, including the risks of thrombosis associated with immune checkpoint inhibitors as compared to those with traditional systemic therapy, associated risk factors, and the optimal prevention and treatment strategies.

Keywords: venous thromboembolism ; arterial thrombosis ; cancer-associated thrombosis ; immune checkpoint inhibitors ; anticoagulation

1. Introduction

Patients with cancer have a 12-fold increased risk of venous thromboembolism (VTE) compared to the general population, with the risk further increased to 23-fold in patients receiving chemotherapy or targeted therapy [1]. Cancer-associated thrombosis is linked with significant morbidity that could lead to hospitalizations, delay in cancer treatment, and even mortality. As a result, thromboembolism is the second leading cause of death in cancer patients [2]. Many factors can contribute to the increased risk of thrombosis in patients with cancer, including tumor-related factors such as type and stage of malignancy; patient-related factors such as age, history of VTE, obesity, or other co-morbidities; and treatment-related factors such as surgery or systemic anticancer therapies [3].

In recent years, immune checkpoint inhibitors (ICIs) have revolutionized the landscape of oncology treatment. ICIs are monoclonal antibodies that target proteins that negatively regulate the immune system called immune checkpoints, including programmed cell death (PD)-1 and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) [4]. PD-1 and CTLA-4 are typically expressed on T cells and bind to PD-1 ligands on tumor cells and CD80/CD86 on antigen-presenting cells, respectively. This leads to T cell inactivation to keep the immune response in check [4]. However, tumor cells also commonly utilize this pathway to escape the immune system. Blocking these pathways results in the activation of T cells to target and kill tumor cells [4]. The United States Food and Drug Administration (FDA) approved the first ICI in 2011; by 2020, seven ICIs had been approved by the FDA in at least 15 cancers, and patients eligible for ICIs significantly increased from 1.5% in 2011 to 43.6% in 2018 [5][6]. They have become a mainstay of treatment and are widely used in various cancers, including non-small cell lung cancer (NSCLC), melanoma, renal cell carcinoma, head and neck cancer, and more. Available ICIs target PD-1 (nivolumab, pembrolizumab, cemiplimab) or its ligands (atezolizumab, avelumab, durvalumab) as well as CTLA-4 (ipilimumab). ICIs are known to be associated with a wide range of immune-related toxicities, including gastrointestinal, skin, thyroid, or hematological findings such as autoimmune hemolytic anemia or thrombocytopenia.

Thrombosis had not been a commonly reported adverse event in initial phase III clinical trials leading to the approval of ICIs. However, after the routine clinical use of these agents, multiple studies started to report concerns for thrombosis, although rates varied widely. Data were also conflicting on whether ICIs were indeed associated with a higher risk of thrombosis than traditional chemotherapy.

2. Mechanism of Thrombosis Related to Immune Checkpoint Inhibitors

While the exact mechanisms of thrombosis associated with ICIs remain to be elucidated, several pathways have been considered. Immune checkpoint blockage has been demonstrated to be associated with a pro-inflammatory state and elevated levels of inflammatory cytokines [7]. Furthermore, mouse models showed that PD-1 played a crucial role in

downregulating pro-atherogenic T cells, and blockage of PD-1 could accelerate atherogenesis with increased infiltration of macrophages and pro-inflammatory T cells in atherosclerotic plaques and enhance vascular inflammation and atherosclerosis [8][9]. The promotion of atherosclerotic plagues after ICI use was demonstrated in pre-clinical animal models and could potentially contribute to the increased arterial thrombotic events [10].

In addition, activated T cells can induce synthesis of tissue factor in monocytes and macrophages [11] and is hypothesized to be one of the mechanisms that promote hypercoagulability [12]. To further delineate the pathogenesis of ICI-associated VTE, Roopkumar et al. analyzed pre-ICI blood samples from 15 individuals who subsequently developed VTE on ICIs compared to 10 without VTE on ICIs [13]. In patients who developed a VTE, they found a significant increase in the numbers of total myeloid-derived suppressor cells (MDSCs) and elevated levels of inflammatory biomarkers, including CXCL8 (chemokine ligand), soluble vascular cell adhesion molecule 1, and clustering of other inflammatory cytokines including IL-1β, IL-6, TNF prior to ICI. The potential link between MDSCs and thrombosis is intriguing and could be related to platelet activation triggered by MDSCs, as found in an in-vitro study when MDSCs were exposed to metastatic tumor cells [14], as well as in other thromboinflammatory disorders such as the recent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-1) infection [15]. MDSCs can also release neutrophil extracellular traps (NETs) induced by CXCL8-involved pathways and contribute to a heightened risk of thrombosis [13][16]. Moreover, the elevation of other cytokines is hypothesized to cause activation of endothelium and platelets and activate the pathologic process of immunothrombosis [13][17]. These inflammatory biomarkers could potentially be used to identify patients at high risk for VTE on ICIs in the future.

2.1. Treatment of Thrombosis

Treatment of VTE in patients with cancer on ICIs is not different from other cancer-associated thromboses, which has been covered extensively by recent guidelines and review articles [18][19][20]. Direct oral anticoagulants (DOACs) and low-molecular-weight-heparin are currently the main treatment options for cancer-associated thrombosis. Choice of anticoagulants would depend on tumor types (with the associated risk of bleeding complications), additional risk factors (such as thrombocytopenia, the presence of intracranial tumors, etc.), potential drug-drug interactions (DDI), and patient perspectives [18]. Fortunately, since ICIs are monoclonal antibodies, no significant DDIs with anticoagulants are expected or reported to date. However, ICIs may be used concurrently with other anticancer therapies or supportive care medications, which could still have potential DDIs, and therefore evaluation of DDIs among all concomitant medications remains advisable.

The optimal treatment of arterial thrombosis in patients with cancer is less clear as data are even scanter. Standard-of-care similar to what is provided for the non-cancer population is typically employed, including the utilization of antiplatelet agents with or without anticoagulation, modification of cardiovascular risk factors such as control of blood pressure, diabetes, smoking cessation, etc., and/or revascularization when indicated.

2.2. Survival and Thrombosis in Patients Receiving Immune Checkpoint Inhibitors

In patients receiving ICIs, several studies have shown that the occurrence of thrombosis was associated with worsening survival [21][22][23][13][24] while others have not [25][26][27] (**Table 2**). Possible explanations of worse survival in patients who developed VTE include that thrombosis is an indicator for more advanced cancer stage, worse prognosis, poorer performance status, and/or thrombosis or anticoagulation-related mortality.

Pre-clinical studies have demonstrated that coagulation factors such as factor X can help tumors escape the immune system [28]. Factor X inhibitors such as rivaroxaban were shown to enhance the effects of ICIs and immunity against tumor cells and inhibit tumor growth in mice models [28][29]. It is of great interest whether this finding can be translated into a clinical setting. However, a recent retrospective study showed no difference in response rates, progression-free or overall survival in patients receiving ICIs and therapeutic anticoagulation compared to patients who were not on anticoagulation [30]. Of note, anticoagulation included in this study was not limited to factor X inhibitors (including dabigatran, rivaroxaban, apixaban, enoxaparin, and warfarin). Moreover, the cohort of patients on anticoagulation in the study was significantly older, with poorer performance status, and a higher percentage had lung cancer, all of which were poor prognostic factors [30]. The authors performed a multivariable analysis to adjust for confounders and reached the same conclusions, but residual confounding could be present. More studies with larger sample sizes are needed.

Table 2. Thrombotic outcomes and risk factors in patients on immune checkpoint inhibitors in included studies.

Study	Study Design	N	Follow Up [Median (IQR), Unless Specified]	VTE Incidence (%, 95% CI)	ATE Incidence (%, 95% CI)	Risk Factors for Thrombosis	Comments
Hegde et al. 2017 [31] abstract	Retrospective	76	10.8 mo	18.4	2.6	Female	VTE after ICI did not affect survival, but before ICI did
Ibrahimi et al. 2017 [32] abstract	Retrospective	154	7 mo (198 days)	10.4	0	N/A	VTE was not associated with progression-free survival
Hsu et al. 2018 [33]	Retrospective	50	N/A	2	N/A	N/A	Focused on survival and toxicity No follow up duration nor how VTE assessed
Bar et al. 2019 [21]	Retrospective	1215	12 mo	AVE (including MI, stroke, PE, multisite DVT): 6 mo: 2.6 12 mo: 3.0 AVE plus single site DVT: 6 mo: 4.9 12 mo: 5.8		• NSCLC • History of AVE • Hypertension • Dyslipidemia	AVE was associated with worse survival Rate of AVE was similar in ICI vs. chemo vs. ICI+chemo in lung cancer
Nichetti et al. 2019 [22]	Retrospective analysis from prospective APOLLO cohort	217	37.8 mo	7.4	6.5	• Current smoker • PD-L1 > 50% • Not: • KS • Anticoagulant or antiplatelet agents	TE is associated with worse survival after TE
Ando et al. 2020 [34]	Retrospective	122	N/A Time to thrombosis 90 days (range 6–178)	4.1 Likely 6 mo rate	4.9	History of TE	No follow up duration, unclear definition of TE
Drobni et al. 2020 [35]	Retrospective	2842	2 years	N/A	Composite: 5.35/100 person-yrs MI: 2.49 Stroke: 2.08	Overall study: ICIs, age, h/o stroke, diabetes, hypertension, NSCLC, male, history of radiation	ICI was associated with increased risk of composite cardiovascular events Statin and steroids attenuated atherosclerotic plaque progression

Study	Study Design	N	Follow Up [Median (IQR), Unless Specified]	VTE Incidence (%, 95% CI)	ATE Incidence (%, 95% CI)	Risk Factors for Thrombosis	Comments
Deschˆenes-Simard et al. 2021 [25]	Retrospective	593	12.7 (4.9–22.7) mo	9.9 (7.5–12.3) 76.5 (59.9–97.8) per 1000 person-years	1.3	• Age < 65 • Higher PD-L1 level • Smoking • <12 mo from diagnosis to ICIs	VTE was not correlated with survival
Gutierrez-Sainz et al. 2021 [26]	Retrospective	229	9.8 mo	7 (4–10)	N/A	• Female • Melanoma	VTE was not an independent factor for shorter survival
Guven et al. 2021 [27]	Retrospective	133	10.1 (5.8–18.5) mo	11.3	N/A	• ECOG ≥ 1 Not: • KS	Median survival numerically shorter in VTE patients, not significant
Icht et al. 2021 [36]	Retrospective	176	6 mo (187 days)	4.5 (2.1–8.3)	N/A	Not: KS	VTE was associated with death
Kewan et al. 2021 [37]	Retrospective	552	12.1 mo	12.1	1.3	• AC use at the time of ICIs (univariable) Not: • KS	Median time to VTE 3.8 mo KS predicts overall survival
Madison et al. 2021 [38]	Retrospective	6143 *	6 mo	6.3	2.6	N/A	ICIs were associated with higher risk of thrombosis compared to chemo alone but not significant in multivariable analysis
Moik et al. 2021 [23]	Retrospective	672	8.5 mo	6 mo: 5.0 (3.4–6.9) Overall: 12.9 (8.2–18.5)	6 mo: 1.0 (0.4–2.0) Overall 1.8 (0.7–3.6)	• History of VTE Not: • KS	VTE (after ICI) was associated with worse survival
Mulder et al. 2021 [1]	Population cohort	370	12 mo	6 mo: 4.1 (2.3–6.7) 12 mo: 7.1 (4.2–11.1)	N/A	N/A	N/A
Roopkumar et al. 2021 [13]	Retrospective	1686	438 days (range 7–1971)	6 mo: 7.1 12 mo: 10.9 Overall: 24	N/A	• Younger age • Metastasis • Biomarkers	VTE was associated with worse survival No difference in VTE incidence with types of ICIs

Study	Study Design	N	Follow Up [Median (IQR), Unless Specified]	VTE Incidence (%, 95% CI)	ATE Incidence (%, 95% CI)	Risk Factors for Thrombosis	Comments
Sussman et al. 2021 [24]	**Retrospective**	**228**	**27.3 mo**	**6 mo: 8.0 (4.9–12.0) 12 mo: 12.9 (8.9–17.7)**	**6 mo: 2.2 (0.84–4.8) 12 mo: 4.5 (2.3–7.8)**	• Combination ICI • KS ≥ 1 • History of CAD • Anticoagulation at treatment start	**VTE was associated with worse survival**
Moik et al. 2021 [39] **abstract**	**Population cohort**	**3259**	**24 mo**	**6 mo: 3.9 (3.3–4.7) 12 mo: 5.7 (4.9–6.6) 24 mo: 7.3 (6.2–8.4)**	**6 mo: 1.3 (0.9–1.8) 12 mo: 2.2 (1.7–2.8) 24 mo: 3.1 (2.4–3.8)**	**N/A**	**Use of ICI was associated with 1.5 to 6.5 fold increased odds of VTE**

* including N = 2685 for ICIs alone, and N = 3458 for ICIs plus chemotherapy, median age reported by groups (ICIs alone or ICIs plus chemotherapy). Abbreviations: ATE—arterial thrombosis; AVE—acute vascular events; CAD—coronary artery disease; DVT—deep vein thrombosis; ECOG—Eastern Cooperative Oncology Group; h/o–history of; ICIs—immune checkpoint inhibitors; IQR—interquartile range; KS—Khorana score; MI—myocardial infarction; mo—months; N—number of patients included; N/A—not available; NSCLC—non-small cell lung cancer; PE—pulmonary embolism; TE—thromboembolism; VTE—venous thromboembolism.

3. Conclusions

ICIs have become the main treatment strategy in cancer and result in prolonged survival. Recent observational studies have shown concerns for increased risks of both venous and arterial thromboses in patients receiving ICIs than previously perceived, and patients with thromboembolic complications while on ICIs had also been shown to have worsened survival in some studies, but whether the risks are higher compared to those associated with chemotherapy remain unclear. It is important for clinicians to be aware of the potential thrombotic complications, to educate patients and recognize signs and symptoms of thrombosis, to allow prompt treatment if needed and avoid complications. Future research to evaluate risk factors and develop robust risk assessment models to allow risk stratification and effective utilization of thromboprophylaxis in this population is needed. Furthermore, whether the concurrent use of anti-Xa inhibitors, aspirin, or statins can enhance the effects of ICIs and lead to better antitumor effects and survival is of great interest.

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