



## Immune Checkpoint Inhibitors and Car-T Cell Therapy: Thrombotic and Vascular Complications

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### Abstract

**Background:** Due to the different genetic properties of malignant neoplasms and their tendency to cause the formation of blood clots, the risk of these complications is much higher than in the general population. There is even a higher risk of blood clots forming during chemotherapy or hormone therapy for cancer.

**Aim:** This paper will summarise publications to gain a better understanding of the risks of blood clots associated with checkpoint inhibitors and CAR-T cell therapy of cancer. The review will also address potential problems and guide how to address them. Even when used on their own, checkpoint inhibitors can cause blood clots, albeit at a lower rate than chemotherapy; however, this assumption has not been definitively proven, as ICI-type agents are rarely given to cancer patients as monotherapy (or if given, these cancers baseline thrombogenicity is less active sui generis). The incidence of these problems varies depending on the type of disease, patient characteristics and somewhat on immunotherapeutic drug selection itself. It is important to inform doctors who prescribe these treatments of this fact and try to provide ideas which may help make good individual decisions. The anticoagulant prophylaxis is probably indicated in many such cases, even with monotherapy in cancer. However, still on a somewhat individual basis, as prospective, multicentre, double blind trials are not available, recommendations are based on some rather anecdotal, or retrospective data in respect of disease type, treatment and patient characteristics and the selection of an optimal anticoagulant prophylactic approach.

**Keywords:** Immune checkpoint inhibitors, CAR-T cell therapy, and thrombosis.

### Introduction

Approximately 105 to 180 out of every 100,000 people are affected by deep vein thrombosis (DVT), which can sometimes lead to pulmonary embolism (PE). This equates to just 0.6% of the population [1,2].

The phenomenon of cancer-associated thrombosis (CAT) has been recognised for around 200 years. The rate of VTE among cancer patients is 8–10 times higher than in the general population. There are many risk factors for CAT, including the type of cancer, the patient's biological characteristics, and the treatment methods. Around 20–30% of VTEs are CAT-related. CAT accounts for 15% of cancer diagnoses in the first year, a figure which then decreases by 6% each year. 4% [3].

Irrespectively to the type of solid tumour, its stage and particular genetic subtypes, it is widely accepted standard approach that anticoagulant prophylaxis is mandatory to reduce or prevent systemic treatment-associated VTE during chemotherapy or chemo- plus hormonal therapy or perioperative periods [3-7].

**Predictive CAT Score:** The Khorana score was identified as a significant instrument for evaluating the risk of chemotherapy-associated VTE and cardiotoxicity in tumours [8]. The Khorana score is based on five types of risk factors, each assigned a specific point value. Site of cancer: Very high-risk sites (e.g. stomach or pancreas) are assigned 2 points; high-risk sites (e.g. lung, lymphoma, gynaecological, bladder or testicular) are assigned 1 point; and other sites are assigned 0 points. Platelet count:  $\geq 350,000/\mu\text{L}$  receives 1 point. Haemoglobin levels: under

100 g/L. White blood cell count:  $>11,000/\mu\text{L}$  receives one point. Body Mass Index (BMI):  $\geq 35 \text{ kg/m}^2$  receives 1 point. The total score is calculated by summing the points for each risk factor, with higher scores indicating a greater risk of VTE. The fact that this score system was created before ICI treatments were used in clinical practice should also be noted. However, it is still a useful tool for assessing the CAT risk in patients [8].

### **Modern Immunotherapeutic Approaches as A Single Agent or Combined with Chemo (Hormonal) Therapy**

The following part of this review will cover some important data, mostly on the so-called Immuno checkpoint inhibitors (further on abbreviated as ICI), i.e. PD-1 inhibitors, PD-1 ligand inhibitors, CTLA4 inhibitors and briefly on CAR-T cell therapy and thrombotic and vascular events and their prevention. Due to the lack of availability of controlled trials in respect of CAT and ICI administration, the new generation of ICI-type (cemiplimab, atezolizumab, avelumab, durvalumab) or LAG-3 type agents (retilimab, opdivo) or other CTLA-4 targeting agents (tremelimumab) will not be discussed this time. These approaches were seriously analysed, according to the fact that they revolutionised cancer therapies, and with respect of the vascular and thrombotic sequelae, publications reached the necessary threshold to realise and judge risks and indicate prophylaxis accordingly [7,9].

These new immunotherapeutic approaches in monotherapy are probably less thrombogenic than traditional antitumour therapeutic modalities, which induce greater tumour lysis, but their use in first-line monotherapy is rather limited, mostly with cancers with a lower Khorana score, so this statement is not clear-cut evidence so far. In higher score cases and as part of chemo-combination, they are capable of inducing extra thrombotic and vascular untoward events, depending on individual properties, disease type and stage, etc., which deserve special attention [10,11].

#### **a. ICIs: PD-1, PD-1 ligand. Pathogenesis of thrombotic and vascular events, main properties and data about the events**

Pathogenesis, briefly: ICIs may trigger complex, potentially dual-edged platelet activation around the tumour. This could be beneficial for inducing local platelet activation and tumour invasion inhibition through microvascular thrombosis. However, systemic prothrombotic effects might also develop from these events [12,13]. Furthermore, the T cell CD8<sup>+</sup> activation in itself also activates platelets, may provoke autoimmune phenomena and probably most importantly activates Tissue Factor, which leads to increased activity of the extrinsic side of blood coagulation, and may accelerate and predispose to induce CAT events, along with elevating FVIII activity and possibly reducing protein S activity [14,15]. Increased inflammation and

endothelial cell activation is a common features observed during ICI-type therapies. These phenomena probably play a definitive role in ICI-induced multifaceted autoimmune reactions (colitis, myocarditis, colitis, inflammatory bowel disease and myocarditis, and heparin thrombocytopenia-like events), too [16,17].

During neutrophil activation, the so-called neutrophil TRAPS might also be generated; they sometimes interact with activated T cells, and trapping of platelets and other coagulation factors and this way they probably increase thrombogenicity. Fibrinolysis also seems to be reduced in some cases. In addition to that, surplus amounts of the so-called Myeloid Derived Suppressor Cells are also capable of increasing platelet endothelium activation procedures, which in turn usually induces cytokine release, also promoting blood clotting [17-19].

#### **b. Clinical experiences (anecdotal, case reports, retrospective data, meta-analysis, etc.)**

Arterial and venous central catheter thrombosis had been described with PD-1(ligand) inhibition [19]. The Vienna group made a comprehensive analysis of VTE and clinical course with ICI-treated cancer patients, concluding to a relatively strong correlation with these therapeutic modalities [20]. A Spanish group came to a similar conclusion, finding more VTE in patients who received ICI or CTLA-4 inhibitor therapies in melanoma treatment protocols [21].

The Khorana group made a systematic analysis of non-small cell lung cancer-treated patients. Most VTE appeared in the chemo group, somewhat less in ICI-immune +chemo combinations, and even less, but still some in the ICI monotherapy cohort of patients [22]. Another systematic analysis had also been performed about the risk factors that may increase the chance of VTE (cardiac events) in ICI-treated cancer patients: they were cancer stage, tumour lysis, combination with chemo, previous VTE or arterial thrombosis and thrombophilic patients [22]. Their cumulative analysis showed 7-8% VTE and 1-5% arterial thrombosis within the 1st year of cancer patients receiving ICIs, so they urged for gaining more data and considering prophylactic anticoagulant antithrombotic therapies, including platelet function inhibition, if platelet counts allow it [22].

Another large, detailed, multicentric, valuable even if retrospective analysis had been published by Gong et al. [23], analysing 2854 cases. They were following post-ICI patients for more than 194 days, and the adjusted VTE rate was higher after starting ICI 259 VTE as opposed to 244 in non ICI controls. There were more lower limb cases and pulmonary emboli, as well. VTE incidence was highest right after initiation of ICI-containing protocols. The absolute risk for VTE was 7,4% at 6 months, and 13,8% at 1 year. They extended the Khorana score to

indicate risk by hypertension, smoking, diabetes, chronic kidney disease, previous coronary revascularisation or ischemic stroke, and previous VTE. They also gave detailed data on tumour type and chemotherapy types. In contrast to the Khorana score, they found more cases with slightly younger patients (under 65 years), too. Immune-related adverse events were between 4,5-23% in different cohorts of patients. Mean Khorana score was 1,36 in their analysis. Melanoma cases were rarely followed by VTE compared to other cancers. Different ICI classes or types of drugs were neutral with respect of CAT problems. Cardiovascular problems were present before ICI administration in 10-14% hypertension (49%), and ICI combination induced vascular events mainly in patients with a previous cardiovascular background, and it also increased the risk of CAT, VTE. Some de novo post-ICI coronary disease and other arterial thrombotic vascular events during ICI administration had also been observed. They did not give a definitive answer, if ICI+chemo combination is much more thrombogenic than chemo alone, but certainly their study had bias and limitations in some respects (for example, pulmonary embolism diagnostic approaches were heterogeneous, VTE diagnostics were not quite homogenous, and the followup of other vascular events were not standardised, a retrospective fashion, historical control group, etc. [21,22,23].

CTLA-4 inhibitors, thromboembolic and vascular complications might sometimes be more severe or common than ICI [25]. More thrombotic events were documented in melanoma immunotherapy cases, whose therapy was usually ipilimumab-containing [25]. Sometimes, even fingertip necrosis might develop during ipilimumab treatment (26). This view is very difficult to translate into clinical actions; it is much more likely that ICI+ CTLA-4 inhibitors in combination possess more cardiotoxicity [26]. Anyhow, some other reports do not support that the ipilimumab and CAT relationship is really significantly different from ICI-based immunotherapies.

### **Hormone administration and checkpoint inhibitors**

Corticosteroid administration may be a part of treatment, mostly against side effects (i.e polytransfused patients, etc.). One might presume it counteracts with immunostimulants (checkpoint inhibitors and CTLA-4), but that assumption is not clarified [27,28]. No doubt, sexual types of hormones might also be an additional VTE-promoting factor. Due to the increased number of heart attacks, there is a recommendation to give aspirin prophylaxis in all cases, but bleeding complications can be dangerous with this approach, especially in patients with low platelet counts or liver abnormalities predisposing to easy bruising [28,29].

So in conclusion, it is clear that ICI, ICI+chemo- (hormonal) cancer treatments are increasing the risk of CAT, heart problems and some other vascular events. It is not completely clear if ICI

monotherapy also carries this risk in a certain degree (conflicting numbers). It also does not completely explored how much extra CAT or vascular events might be linked to ICI (or other immunotherapeutic) combinations. This difference is difficult to establish, as patients had different types and stages of cancers, chemo protocols were also different, and Khorana-type risk categories were mixed [20-24, 30-33].

There is an urgent need to initiate prospective multicenter trials with more homogenous tumour types, stages, chemo subtypes, and standardised diagnostic approaches. It would also be important to have prospective trials with ICI and other immunotherapeutic modalities in lymphoma and cell therapies, too. So it is very important to create a more specific risk score predicting VTE and vascular events with immune checkpoint inhibitor-containing therapies. According to a systematic analysis, the high-risk clinical groups are liver cancer, liver dysfunction, diabetes mellitus, older (or under 65?) age, a large tumour mass, smokers and high Khorana group cases [34].

### **c. CAR-T therapy, T cell activator mono- or bclonal agents in oncohematology, bleeding risk (sometimes predominant), thrombosis, vascular effects)**

CAR-T therapy is typically complicated by cytokine release, inflammatory cytokine storm or hypofibrinogenaemia associated with bleeding and neurological complications. Even if it is a rare event, but bleeding is sometimes capable of inducing consumption-type disseminated intravascular thrombosis [35]. There are some other reports of mixed appearance of bleeding and thrombotic complications, along with multiorgan dysfunction in CAR-T therapies [36].

Complex haematological T cell activator therapies (like Blincyto, or double monoclonal T cell activators) may induce rare CAT and vascular events, as CD8T cells are activated, and may initiate or amplify blood clotting. Due to the different blood counts, frequent thrombocytopenia, hypofibrinogenaemia, and sometimes different lymphoablative pretreatments (or strong immunosuppression in allogeneic bone marrow transplantation) make this issue much more complex, and prolonged thrombocytopenia needs extreme caution with application and timing of anticoagulant or antiplatelet therapeutic modalities [35,36].

### **Anticoagulant, antiplatelet prophylaxis in ICI and/or ipilimumab-containing anti-cancer therapeutic modalities.**

This is a very important pragmatic question to address, which is a must in each case. Decisions need individual evaluation by patients, assessing crucial elements and expected hazards as follows: disease and treatment-related as well as patient-related factors.

## Disease and treatment-associated VTE risk, helping indication of anticoagulant prophylaxis

1. Cancer type, stage, extension, and Khorana score [8]. Pulmonary, pancreatic, stomach and brain tumours carry higher risks than other cancers.
2. Strong pro-prophylaxis argument in treatment if it is chemo-(hormonal combination, in which tumour lysis is strong, and thrombogenic effects are combined and show cumulative properties [21,23,24,33].
3. Prophylaxis should be considered in combined ICI, or even a little bit more in ICI+ ipilimumab cases, even if they are rarely administered without synchronous chemo- or hormonal modalities [20,21,23,31,33,37].

## Patient-related prophylaxis supporting moments

1. previous VTE, genetic thrombophilia (screening is obligatory)
2. Prolonged use of central venous access
3. Existing data on coronary heart disease or other arterial occlusive events, dysfunction, smokers, and diabetes mellitus
4. Presence of antiphospholipid syndrome

Patient-related other anticoagulant-induced complication risk: thrombocytopenia, congenital or acquired bleeding disorders, hypofibrinogenemia, age, and liver failure [38].

## The selection of an anticoagulant agent

The most frequently used tool is LMWH; antiXa is easy to measure, neutralisation is a complex issue, but available, which are strong arguments for LMWH prophylaxis. On the other hand, some observations show better immunotherapeutic antitumour efficiency with rivaroxaban and apixaban when laboratory measurement of efficiency is complicated but available, but the reversal of bleeding complications is less straightforward [33,39].

If the patient had previous coronary heart disease or appear to have de novo coronary heart disease or other arterial vascular disorder, aspirin is probably indicated, very cautiously, depending on platelet counts [40-42].

Even with its heterogeneous and retrospective data makes clear that ICI, along with other cancer immunotherapies, increases (further) the risk of CAT, VTE, and, as a general principle anticoagulation, or if a heart problem is present, antiplatelet prophylaxis has to be considered [42], judging individual risk and benefits, predictive score systems. In oncohematology, even more individual decisions and more cautious interventions are desirable.

Anyhow, there is a great need to start organising multicenter prospective trials in more homogenous patient cohorts to help

create standards and guidelines in indication, anticoagulant antiplatelet drug selection, treatment duration. Until that, the available data provide a solid basis that all patients receiving ICI or other anti-cancer immunotherapy have to be considered as candidates for anticoagulant prophylaxis, after careful evaluations of predictive score, patient historical data, tumour type, planned anticancer therapeutic approach, and probably apply anticoagulant and antiplatelet therapy as an individual but mandatory decision. The complex vascular, hemostatic events following these therapies, case reports are also necessary to publish, providing help for better and more tailored prophylaxis selection [23,24,33,39,42]. It is also an open issue, that the anticoagulant dose or duration should be different IC also administered, probably not, until active anti-cancer treatment is applied (hormonal, chemo-, ICI). Anticoagulant selection is also an exciting question, if immunotherapy is applied, aspirin could be an additional agent, if there are no contraindications. The selection of an antXa agent instead of LMWH may be a good option [43-51].

## List of abbreviations

**BMI:** body mass index

**CAT:** cancer-associated thrombosis

**LMWH:** low molecular weight heparin

**PD-1, PD-1 ligand,** immune checkpoint inhibitors (programmed cell death, or programmed cell death ligand)

**CTLA-4 inhibitor:** an anti-cancer immunological agent

**VTE:** venous thromboembolism

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