THERAPY

Venous thromboembolism risk and immune checkpoint inhibitors: what the literature says.

Patients with cancer have an increased risk of venous and arterial thromboembolism (VTE/ATE) [1]. Several factors have been identified that contribute to this risk [2], some of which are treatment-related risk factors for platinum-based chemotherapy, anti-angiogenic agents, and hormone-based therapy [3,4].

In recent years, immune checkpoint inhibitors (ICIs) have become a mainstay of treatment. They are widely used in the treatment of various cancers, including non-small-cell lung cancer (NSCLC), melanoma, renal cell carcinoma and head and neck cancer [5]. 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) [5].

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 [5].

Large-scale randomized controlled trials evaluating ICIs surprisingly did not provide information on VTE and ATE rates [6].

However, after the routine clinical use of these agents, multiple studies started to report concerns for thrombosis, although rates varied widely [5]. Data were also conflicting on

whether ICIs were associated with a higher risk of thrombosis than traditional chemotherapy.

A recent article reviewed the current literature on venous or arterial thrombosis associated with ICIs [5]. Here, we summarize the key points.

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 [5]. Immune checkpoint blockade has been demonstrated to be associated with a pro-inflammatory state and elevated levels of inflammatory cytokines [5].

A recent study analyzed pre-ICI blood samples from 15 individuals on ICIs who subsequently developed VTE compared to 10 individuals on ICIs who did not develop VTE [5,7]. Patients who developed a VTE showed a significant increase in the numbers of total myeloid-derived suppressor cells 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, and TNF before ICI [5].

Myeloid-derived suppressor cells can trigger platelet activation and release neutrophil extracellular traps, contributing to a heightened risk of thrombosis [5]. Moreover, the elevation of other cytokines is hypothesized to cause activation of endothelium and platelets and activate the pathologic process of immunothrombosis [5].

Incidence of Thrombosis

Venous Thromboembolism

More recent studies report a higher risk of thrombosis for patients with cancer treated with ICIs than previously reported in ICI clinical trials [5].

Considering 18 retrospective studies focusing on VTE and/or ATE in patients receiving ICIs, the cumulative incidence of VTE is approximately 5–8% at 6 months and over 10% at 12 months [5]. Thromboembolic events may be commonly under-reported or under-estimated in oncology clinical trials where the primary goal is to evaluate the effectiveness of anticancer therapies, and thromboembolism is often reported as adverse events (not primary or secondary outcomes) by using Common Terminology Criteria for Adverse Events (CTCAE) [5].

Notably, the risk of thrombosis seems to exist during the entire duration of the treatment with ICIs [5]. Despite chemotherapy, most VTE events occur in the first 6 months; with ICI, most events happen after 6 months of treatment [5]. This is of particular concern since patients receiving ICIs have prolonged survival with ongoing treatment, which increases the duration of exposure to ICIs and the associated risk for thrombosis [5].

As previously said, it is not clear whether ICIs are associated with an increased risk of VTE compared to traditional chemotherapy [5]. Patients receiving ICIs and chemotherapy are usually not directly comparable, and many studies only included patients on ICIs or ICI combinations [5]. Four studies have attempted to compare rates of thrombotic complications in patients receiving ICIs to those receiving chemotherapy. The available

data so far did not show clear differentiation in the rates of thromboembolic events associated with ICIs compared to chemotherapy, although data quality remains poor [5].

Arterial Thrombosis

A few retrospective studies have reported variable rates of ATE, ranging from 1 to 5% at 12 months [5]. Another study showed that ICIs were associated with an increased risk of arterial thrombosis compared to other anticancer therapy [5, 8].

Treatment of Thrombosis

Treatment of VTE in patients with cancer on ICIs is not different from other cancer-associated thromboses [5]. Direct oral anticoagulants and low-molecular-weight heparin are currently the main treatment options for cancer-associated thrombosis [5]. No significant pharmacokinetic drug–drug interactions with anticoagulant and ICIs 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 drug–drug interactions [5].

The optimal treatment of arterial thrombosis in patients with cancer is not clear as data are scant [5]. Therefore, the 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, and/or revascularization when indicated [5].

Prevention of Thrombosis

Specific risk models need to be developed for patients receiving ICI treatment to help risk prediction and tailor thromboprophylaxis if needed [5]. In fact, the risk models available today, like the Khorana score, are not validated or predictive for patients receiving ICIs [5].

For primary prevention of arterial events, the standard of care as in non-cancer population can be of benefit, including careful assessment of cardiovascular risk factors, such as smoking, obesity, hypertension, hyperlipidemia, diabetes, and aggressive modification of these risk factors with lifestyle change or medications, such as statins [5].

Conclusion

Recent observational studies have shown concerns for increased risks of venous and arterial thromboses in patients receiving ICIs than previously perceived [5]. In some studies, patients with thromboembolic complications while on ICIs had also been shown to have worsened survival, but whether the risks are higher than those associated with chemotherapy remains unclear [5].

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 [5].

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