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Anticoagulation and thrombocytopenia in cancer: what more can we learn from existing randomized controlled trials

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In this issue of Haematologica, Patell and colleagues¹, present a post-hoc analysis of the Hokusai VTE Cancer study, a randomized phase III trial comparing edoxaban with dalteparin for treatment of acute venous thromboembolism (VTE) in patients with cancer². The aim was to evaluate the outcomes of major bleeding, clinically relevant non-major bleeding (CRNMB), recurrent VTE, and survival, in cancer patients with thrombocytopenia (TP) (i.e., platelet count <100 K/µL at one or more specified time points during the trial) who were undergoing anticoagulation for acute VTE. The results show that patients with TP experienced significantly higher major bleeding (9.0% vs 4.0%, SHR=2.4 [1.19-5.06]) and CRNMB (17.9% vs 9.6%, SHR=2.0 [1.21-3.32]) than patients without TP. In addition, TP did not reduce recurrent VTE (9.8% vs 7.4%, SHR=1.3 [0.7-2.6]).

In a group of patients with TP and gastrointestinal (GI) cancer the rate of major bleeding was higher with edoxaban compared to dalteparin (16.8% vs 0%), whereas in patients with TP and haematologic malignancies this rate was higher with dalteparin compared to edoxaban (19.0% vs 0%).

Thrombocytopenia exposes patients to bleeding complications and represents a relevant limiting factor for use of antithrombotic medications, which are often required in malignant disease due to the increased risk of both venous and arterial thrombosis³. Notably, the presence of thrombocytopenia is not protective of VTE⁴.

In cancer patients, TP is rather frequent, as a result of the bone marrow primary or secondary involvement by malignant disease or as a consequence of anti-cancer treatments. A thoughtful balance between the severity of TP and the need for anticoagulation must be accomplished when TP occurs in patients with an acute VTE event or in those who are already on chronic anticoagulation for one known indication (i.e., prevention of stroke in atrial fibrillation, or recurrent VTE). In those scenarios, both the thrombotic and bleeding risks of the individual patient should be carefully considered (Figure). The perception of a prevailing bleeding risk supports the decision from physician to hold or reduce the dose of antithrombotic drugs. Differently, the perception of a high thrombotic risk drives the decision towards continuing antithrombotic therapy at a full or reduced dose with or without supportive platelet transfusions ⁵. As reviewed recently⁶, the results of a number of randomized controlled trials (i.e., HOKUSAI VTE, SELECT-D, ADAM-VTE, CARAVAGGI0, CANVAS, and CASTA-DIVA studies) have consolidated the recommendation by International guidelines⁵⁷ for use of anti-Xa direct oral anticoagulants (DOACs) as a first line option for
treatment of cancer-associated VTE. However, there are still areas of uncertainties, particularly for use of these drugs in presence of concomitant thrombocytopenia. Available evidence suggests that in mild to moderate TP (i.e., 100-50 K/µL platelet) full-dose anticoagulation in patients with cancer-associated VTE is generally safe\textsuperscript{8}, however, according to recent EHA guidelines\textsuperscript{9}, when TP is not stable and is expected to drop < 50 K/µL in the next days to weeks, low molecular weight heparin (LMWH) should be preferred over DOACs and VKAs. Furthermore, due to lack of data, these guidelines recommend against use of DOACs in conditions of severe TP (i.e., < 50 K/µL). Given the increasingly widespread use of DOACs for treatment of VTE in patients with cancer, the need to manage this type of anticoagulation in TP cancer patients may occur with growing frequency, and it is therefore important to determine the behaviour of DOACs and possible dose-adjustments in this specific setting.

As the current guidelines on TP and anticoagulation in cancer patients are mainly based on consensus guides and expert opinions, with their work, Patell and colleagues give a great impulse, that should be followed by others, to improving evidence-based decisions by clinicians. Indeed, up to now there are no ad-hoc studies or RCTs to test strategies of anticoagulation in cancer patients with TP, to the opposite thrombocytopenic cancer patients are often excluded from enrollment in trials testing efficacy and safety of anticoagulant drugs. Therefore using available data collected from prospective registries, as done by the investigators of the TROVE study\textsuperscript{10}, or using post-hoc analysis of existing phase III randomized clinical trials investigating DOACs for cancer-associated VTE treatment, as done by this post-hoc analysis, are currently the best possible approaches to take a step forward. Although these studies have limitations in that they have enrolled a small percentage of patients with TP and have excluded severe TP forms, they still provide interesting information on mild-moderate TP. These data will help laying the foundation for future clinical studies that, due to consistent sample size and high quality, will be able to dictate specific strategies for management of thrombocytopenia in patients with cancer-associated VTE, who are receiving all different types of anticoagulant drugs, including DOACs.
References

Figure legend

Anticoagulation + thrombocytopenia in cancer patients: Evidence from the HOKUSAi VTE post-hoc analysis.

CRNMB: clinically relevant non major bleeding. TP: thrombocytopenia, VTE: venous thromboembolism.
Clinical scenarios of cancer patients with thrombocytopenia and indication for anticoagulation

New onset thrombocytopenia in patients on chronic anticoagulation

Thrombocytopenia

Need of anticoagulation

New onset thrombotic event in thrombocytopenic patients

Results from the analysis by Patell et al.

Major bleeding and CRNMB risk increases in anticoagulated TP patients

- Gastrointestinal cancer: Edoxaban highest risk
- Hematological cancer: Dalteparin highest risk

Recurrent VTE risk does not decrease in anticoagulated TP patients

No difference between TP and non-TP patients