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 colleagues,[1] 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 cancer.[2] 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 <100x10^6/L 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%, sub-distribution hazard ratio [SHR]=2.4, 95% confidence interval [CI]: 1.19-5.06) and CRNMB (17.9% *vs*. 9.6%, SHR=2.0, 95% CI: 1.21-3.32) than patients without TP. In addition, TP did not reduce recurrent VTE (9.8% *vs*. 7.4%, SHR=1.3, 95% CI: 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 hematologic malignancies this rate was higher with dalteparin compared to edoxaban (19.0% *vs*. 0%).

TP 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 thrombosis.[3] Notably, the presence of TP is not protective of VTE.[4]

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 1). The perception of a prevailing bleeding risk supports the decision by 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 recently,[3] the results of a number of randomized controlled trials (i.e., HOKUSAI VTE, SELECT-D, ADAM-VTE, CARAVAGGIO, CANVAS, and CASTA-DIVA studies) have consolidated the recommendation by international guidelines[6,7] for the use of anti-Xa direct oral anticoagulants (DOAC) as a first line option for treatment of cancer-associated VTE. However, there are still areas of uncertainties, particularly for the use of these drugs in the presence of concomitant TP. Available evidence suggests that in mild to moderate TP (i.e., 50-100x10^6/L platelet) full-dose anticoagulation in patients with cancer-associated VTE is generally safe,[8] however, according to recent European Hematology Association guidelines,[9] when TP is not stable and is expected to drop <50x10^6/L in the next days to weeks, low molecular weight heparin (LMWH) should be preferred over DOAC and VKA. Furthermore, due to lack of data, these guidelines recommend not to use DOAC in conditions of severe TP (i.e., <50x10^6/L). Given the increasingly widespread use of DOAC 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 DOAC 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 improve evidence-based decisions by clinicians. Indeed, up

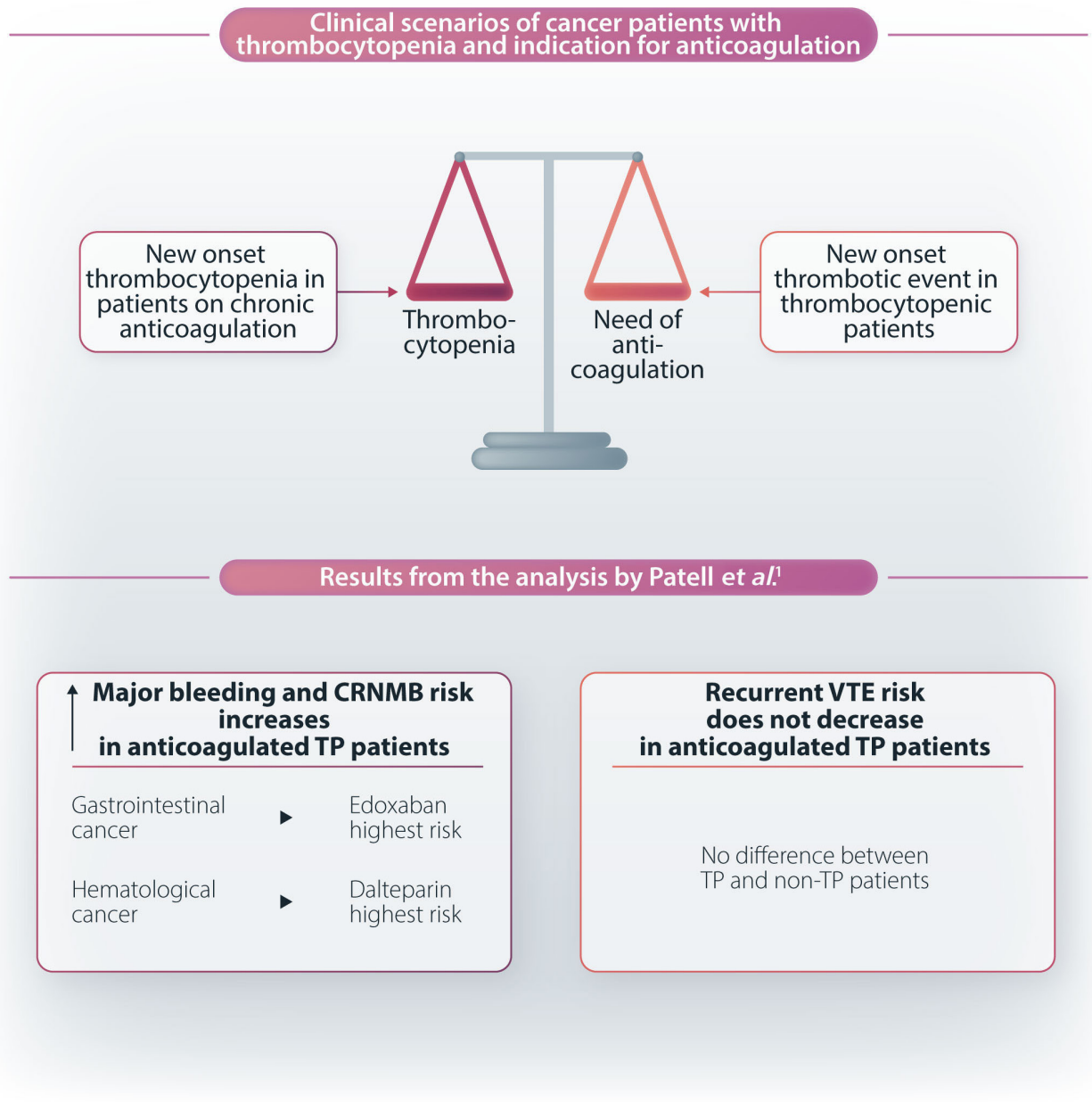

Figure 1. Anticoagulation plus thrombocytopenia in cancer patients: evidence from the HOKUSAI VTE *post hoc* analysis. CRNMB: clinically relevant non-major bleeding; TP: thrombocytopenia; VTE: venous thromboembolism.

to now there are no *ad hoc* studies or randomized clinical trials to test strategies of anticoagulation in cancer patients with TP, to the opposite thrombocytopenic cancer patients are often excluded from enrolment 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,[10] or using *post hoc* analysis of existing phase III randomized clinical trials investigating DOAC 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 to lay the foundation for future clinical studies that, due to consistent sample size and high quality, will be able to dictate specific strategies for the management of TP in patients with cancer-associated VTE, who are receiving all different types of anticoagulant drugs, including DOAC.

Disclosures

No conflicts of interest to disclose.

Contributions

Both authors contributed equally.

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