Title: Platelet counts and risk of major bleeding with ibrutinib

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Dear Editor,

We have read the paper by Mock et al.[1] assessing the risk of major bleeding in a cohort of real-life patients receiving ibrutinib with great interest. Their findings prompt serious concerns regarding major bleeding risk, particularly among patients that were excluded from the population of trials which are the cornerstone of the ibrutinib use today due to need for concomitant therapies. However, these patients surely exist in the real-life setting as shown in the present study.

Although seemingly counterintuitive, platelet counts <50 K/µL did not seem to be associated with higher major bleeding risk in the univarate analysis and were not considered further in the multivariate setting. As shown in the Table 4, platelet counts were not significantly associated with unwanted outcome [HR 1.8, 95% confidence interval (0.4 – 8.3)], although hazard associated with thrombocytopenia was non-significantly increased on average. It is logical and biologically plausible that lower platelet counts would predispose to major bleeding risk, especially if platelet function is blunted by the use of ibrutinib. In our opinion, protective effects of higher platelets in the current study could be abolished by the concurrent use of antiplatelet and anticoagulant drugs which commonly occurs only in a subgroup of patients with adequate platelet counts (i.e. >50 K/µL). Lower platelet counts are a general contraindication for full dose anticoagulant therapy[2] and both antiplatelet and anticoagulant drugs are highly likely to be avoided in this context. Thus, presented lack of association of platelet counts with major bleeding risk is very likely to be confounded by concurrent medications predominantly used only in patients with higher platelet counts. Reported finding should by no means be interpreted as a safe level of thrombocytopenia regarding bleeding risk.

We consider that presented work provides valuable insight into the real-life profile of patients receiving ibrutinib. It also highlights unacceptably high major bleeding risk in a subgroup of patients exposed to ibrutinib, antiplatelet and anticoagulant therapy at the same time. We feel that assessment of factors associated with bleeding risk would benefit from providing additional information regarding proportions of patients with platelet counts >50 K/µL and <50 K/µL receiving concurrent antiplatelet/anticoagulant drugs, how are platelet counts associated with major bleeding risk in subgroups of patients stratified by exposure to these drugs, and whether effects of platelet counts on outcome depend on concurrent anticoagulant/antiplatelet use in the multivariate analysis. We hope that authors could provide such analyses.

References:

1. Mock J, Kunk PR, Palkimas S, et al. Risk of Major Bleeding with Ibrutinib. *Clinical lymphoma, myeloma & leukemia.* 2018;18:755-761.

2. Napolitano M, Saccullo G, Marietta M, et al. Platelet cut-off for anticoagulant therapy in thrombocytopenic patients with blood cancer and venous thromboembolism: an expert consensus. *Blood transfusion = Trasfusione del sangue.* 2018:1-10.