Comment on Lipsky *et al.*: Incidence and Risk Factors of Bleeding-Related Adverse Events in Patients with Chronic Lymphocytic Leukemia Treated with Ibrutinib

We read with interest the recent paper from Lipsky et al. evaluating the potential risk factors for bleeding events in patients with chronic lymphocytic leukemia (CLL) treated with ibrutinib in a phase II study.[1] This study enrolled 85 patients with a baseline platelet count of ≥30 x 10^9/L, and assessed platelet count, vWF activity and antigen levels, factor VIII levels, PT, and aPTT at baseline and on days 2 and 28. Additionally, 66 patients with baseline platelet counts of ≥100 x 10^9/L underwent testing with PFA-100 as a screen for platelet defects. Concordant with recent reports implicating impaired collagen-induced platelet aggregation (assessed by formal platelet aggregation testing) as the likely cause of ibrutinib-associated bleeding,[2-4] the authors performed platelet aggregometry in 12 normal subjects, 14 subjects with treatment-naïve CLL, and 30 ibrutinib-treated subjects with CLL. In contradistinction to earlier reports, Lipsky et al. found that patients with untreated CLL had significant baseline impairments in platelet aggregation to collagen and ADP, and that patients taking ibrutinib had a modest further reduction in collagen-induced platelet aggregation, but an improvement in ADP-induced platelet aggregation.[1] The authors concluded that bleeding in CLL patients treated with ibrutinib occurred because of both CLL- and ibrutinib-related factors.

While this conclusion is compatible with their data, we are concerned it may lead to a simplified perception of "blame the disease, not the drug" when inexperienced prescribers assess and manage ibrutinib-related bleeding risk in individual patients. Remaining mindful of ibrutinib's property as a potent, irreversible anti-platelet drug is highly useful in the clinic, particularly in the management of patients with severe thrombocytopenia and/or taking multiple anti-platelet agents, and in the treatment of patients presenting with acute bleeding or requiring emergency surgery, where transfusion of fresh platelets outside the 3 – 4 hour ibrutinib plasma half-life window completely reverses the bleeding phenotype.[3]

We and others have observed baseline defects in platelet aggregation in patients with CLL.[2,3] However, in our cases the poor aggregation occurred non-specifically across multiple agonists, and were mainly related to thrombocytopenia, as accurate platelet aggregometry requires platelet counts of at least 100 to 150 x 10^9/L when performed using platelet-rich plasma.[2] We note in the Lipsky paper that platelet counts were required to be >100 x 10^9/L for PFA-100 testing, but the platelet counts for subjects tested by whole-blood aggregometry (both CLL control and ibrutinib-treated subjects) were not stated. The platelet count at the time of sample collection is an important component of interpreting platelet aggregation results, and may be especially critical in this study as ibrutinib robustly improves the platelet counts of patients with CLL,[5,6] and it is not known how long after commencing ibrutinib the patients in the Lipsky paper were tested, with a possibility that they may have recovered counts well within the normal range by the time of testing.[1] Potential differences in platelet counts between CLL controls and ibrutinib-treated subjects at the time of testing may explain why there is an apparent recovery in ADP response, and may understate the impact of ibrutinib on collagen-induced aggregation. This issue would be clarified by more detailed information from the authors on their subjects at the time of platelet aggregation testing.

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