The occurrence of trombocythopathy in CLL patients treated with Ibrutinib

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Background

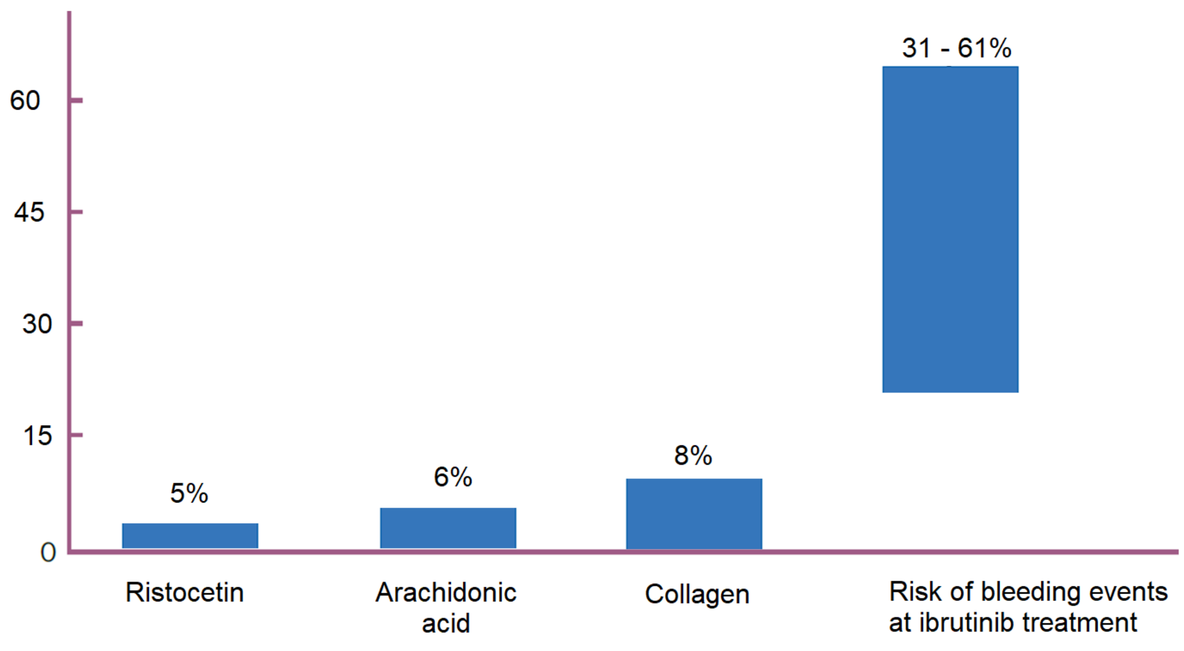
Ibrutinib is an irreversible inhibitor of Bruton's tyrosine kinase that is an effective therapeutic agent for B-cell neoplasms including CLL. Ibrutinib, however, carries an increased bleeding risk due to its effect on several distinct platelet signaling pathways, resulting to thrombocytopathy. Optical agregometry is used for the identification of platelet dysfunction. Platelet-rich plasma (PRP) optical aggregometry using collagen, ADP, ristocetin and epinephrin as inductors is considered the gold standard for examining platelet function. Patients on ibrutinib have reductions in collagen-mediated and ristocetin-mediated platelet aggregation. The degree of inhibition of either collagen- or ristocetin-mediated platelet aggregation in patients on ibrutinib correlates with bleeding. Ibrutinib does not inhibit ADP-mediated platelet aggregation.

Methods

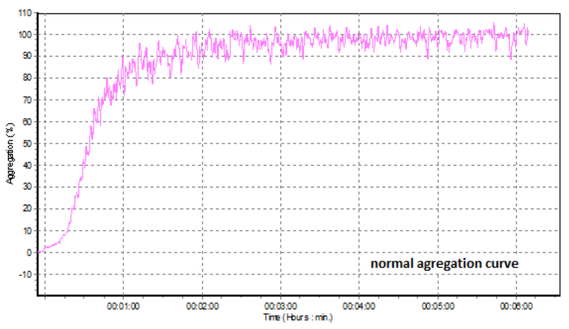
Platelet aggregation using PRP (centrifuging blood specimens onto citrate at 150 x g for 10 minutes at room temperature) was measured in a series of 103 blood samples from 46 CLL patients treated with ibrutinib. Collagen, arachidonic acid and ristocetin were used to induce platelet aggregation. The aggregometer SD Medical TA was used for the measurement. Cut off value for the definition of platelet dysfunction (maximal platelet aggregation) was 60 %.

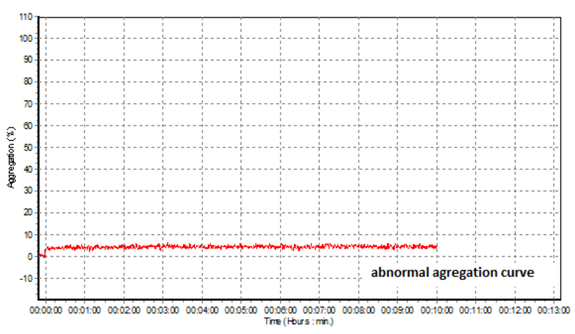
Results

Results of aggregation using PRP are shown in diagrams. Collagen-mediated, arachidonic acid-mediated and ristocetin-mediated platelet aggregation was reduced in 8/103 samples (8 %), in 6/103 samples (6 %) and in 5/103 samples (5 %), respectively. Thrombocytopathy was recognized in only a small proportion of CLL patients treated with ibrutinib.



agregometer SD Medical TA





Conclusion

- ✓ Bruton's tyrosine kinase mediates platelet activation via platelet glycoprotein (GP) VI.
- ✓This can be selectively inhibited by ibrutinib, resulting in clinically apparent thrombocytopathy.
- ✓ In our study, the incidence of platelet dysfunction was 5-8 %. In contrast, the occurrence of bleeding events with ibrutinib is reported 31-61 %. In CLL patients, other factors may explain the variability of bleeding events, including differences in disease type, dosing of the drug, use of other antiplatelet and anticoagulant agents and severity of thrombocytopenia. Individual differences in platelet responsiveness to ibrutinib are also reported.
- ✓ Optical aggregometry represents an objective tool for monitoring of platelet function in ibrutinib treated patients, especially in cases of bleeding.