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641.CHRONIC LYMPHOCYTIC LEUKEMIAS: BASIC AND TRANSLATIONAL

The Mechanism Underlying Lenalidomide-Induced Thrombosis Susceptibility

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Introduction: Lenalidomide, a well-established drug for the treatment of multiple myeloma, significantly enhances patients' survival. Previous clinical studies have demonstrated that its main side effect is an increased risk of thrombotic events. However, the underlying mechanism remains unexplored. Therefore, this study aims to elucidate the mechanism and offer insights into the selection of clinical thrombotic prophylaxis drugs.
Methods: Firstly, we conducted a retrospective analysis of clinical data from 169 newly diagnosed multiple myeloma patients who received lenalidomide. To confirm the impact of lenalidomide on thrombosis formation, FeCl3-induced thrombosis and deep venous thrombosis models in mice were established. To investigate the effects of lenalidomide on platelet function, both in vivo and in vitro experiments were designed.
Results
From January 2013 to June 2021, 169 NDMM patients with VRD as the first-line treatment were included in this study. During our follow-up, 8 patients had TEs **.** TEs included 8 VTE and 1 ATE. There were 7 DVT and 1 PE including in 8 VTE. Among the 8 patients suffering from thrombus, 2 patients did not receive thromboprophylaxis because of low platelet count, and the other 6 patients took aspirin, warfarin and rivaroxaban.
Lenalidomide (25 mg/kg, 50 mg/kg, per day) or vehicle (DMSO) for 14 days were administrated for 2 weeks to healthy male mice. Compared with DMSO group, lenalidomide 25 mg/kg group and lenalidomide 50 mg/kg group significantly affected the formation of venous thrombosis , and there were significant statistical differences in both the length (p=0.002; p=0.0005) and weight (p<0.0001; p<0.0001) of thrombosis. In contrast, the formation of arterial thrombosis was not affected by lenalidomide administration in vivo, occlusion time of experiment group had control group did not have difference, which is consistent with the low incidence of ATE in clinical practice.
To further explore the mechanism, we firstly focused on whether lenalidomide affects platelet function. Compared to baseline data, after taking one cycle of lenalidomide, the mean platelet volume (MPV, p<0.0001), platelet distribution width (PDW, p<0.0001), large platelet ratio (p<0.0001), platelet hematocrit (p=0.0005), and fibrinogen (p=0.0008) of patients increased significantly. To evaluate the effect of lenalidomide on NDMM patient's platelet activation in vitro, we pretreated the washed platelets from NDMM with lenalidomide (5 or 10 um) or DMSO for platelet function assays . There was no difference between the three groups.
To clarify the effect of lenalidomide on platelet function and parameters in vivo, lenalidomide (25 mg/kg, once per day), (50 mg/kg, once per day) or DMSO were administrated for 2 weeks to mice . The last dose was taken the night before narcotism, and platelet function was measured the next morning. We found that different from the changes in platelet related parameters in patients, in vivo data of mice showed no significant changes in platelet count , MPV , PDW , large platelet ratio , and platelet hematocrit after taking lenalidomide.Then we prepared washed platelets from mice for functional experiments. There was no difference between the three groups.
In order to further explore the impact of lenalidomide on coagulation function in NDMM patients, we compared the coagulation parameters of NDMM patients who were enrolled at the time of diagnosis and after one cycle of taking lenalidomide. We found significant differences in prothrombin time, thrombin time, and prothrombin time ratio (**PTR, p<0.0001**), while there was no statistical difference in some changes in activated partial thrombin time (**APTT, p=0.0881**). These results may suggest that lenalidomide promotes the formation of venous thrombosis in vivo by influencing the coagulation pathway.

Conclusions: The administration of lenalidomide had no significant impact on platelet function, which may affect venous thrombus formation by affecting coagulation. Therefore, anticoagulant drugs may be superior to antiplatelet drugs in the selection of clinical thrombus prophylaxis.

Disclosures No relevant conflicts of interest to declare.

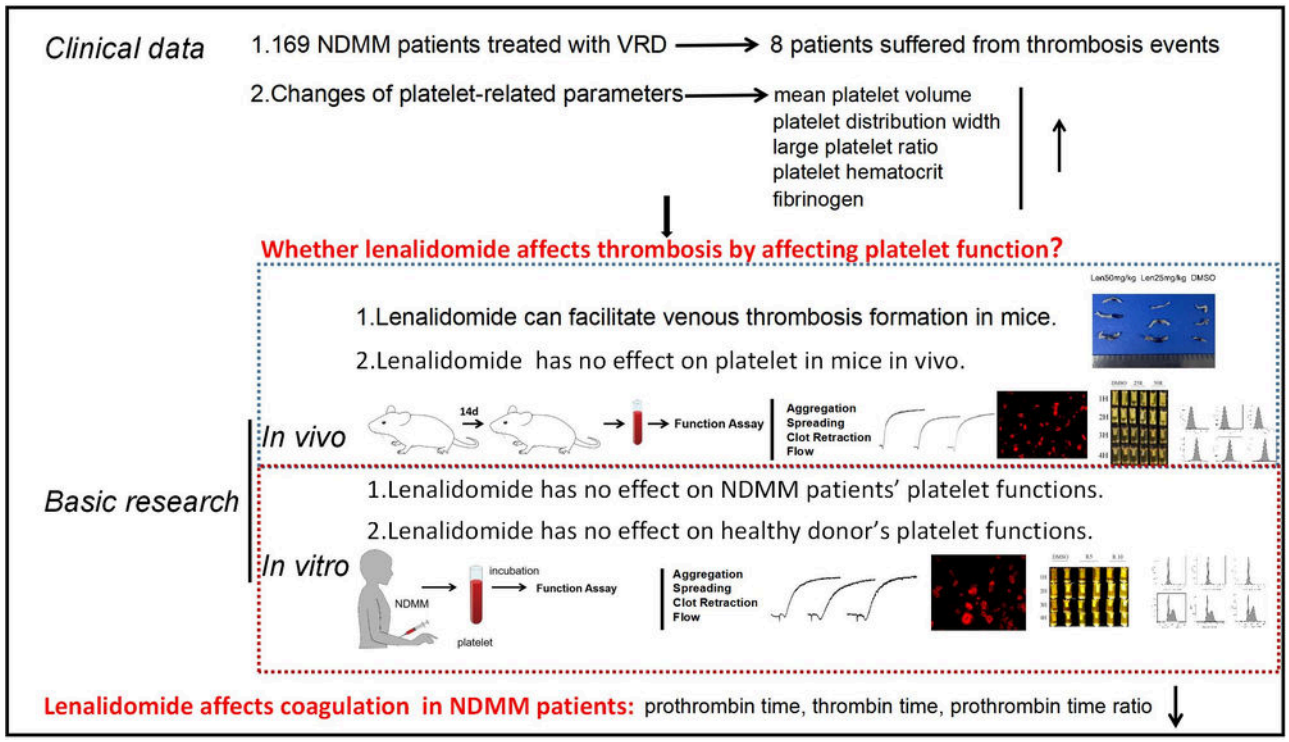

Figure 1

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