Their results suggest that patients with AML harboring mutations in both DNMT3A and IDH2 might benefit from combination treatment with HDAC and prostaglandin synthesis inhibitors when IDH2 inhibitors are not applicable. The findings are highly relevant, because HDAC inhibitors as well as prostaglandin synthesis inhibitors are already available in the clinic.

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THROMBOSIS AND HEMOSTASIS

Comment on Dhanesha et al, page 857

Integrin α9β1: a new target to fight thrombosis

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In this issue of *Blood*, Dhanesha et al explore the role of myeloid cell–specific integrin α9β1 in arterial thrombosis.[1] They demonstrate that genetic ablation or pharmacologic inhibition of the integrin reduces thrombosis and, importantly, this effect is not accompanied by impairment of normal hemostasis.

Integrin α9β1 is expressed on resting neutrophils at a level similar to that of α5 integrin. After activation, its expression increases two- to threefold, and it becomes the most abundant β1 integrin on the neutrophil surface. The role of α9β1 has been demonstrated in such processes as migration on tenascin substrates and vascular cell adhesion molecule 1 (VCAM-1), but no information about its function in thrombosis has been reported so far.

This study demonstrates a novel role of α9β1 on the neutrophil membrane and raises several important questions for further investigation. For example, mechanisms of neutrophil recruitment to the site of thrombus development remain elusive. Fewer neutrophils get recruited to the thrombus in $\alpha 9^{fl/fl}$LysMCre^{+} mice, which suggests that α9β1 binds a ligand on certain cells in the thrombus or in the vessel wall. This integrin binds VCAM-1 on the activated endothelium[2]; however, it is generally assumed that ferric chloride denudes endothelium and therefore VCAM-1 may not be a good candidate for neutrophil recruitment in this model. A potentially dispensable role of endothelial receptors is further confirmed by the clear antithrombotic phenotype in $\alpha 9^{fl/fl}$LysMCre^{+} mice in the laser injury model in which a thrombus grows on a relatively small area of contact with the endothelium.

It is known that α9β1 engagement activates inducible nitric oxide synthase (iNOS), and the resulting nitric oxide (NO) can mediate neutrophil adhesion and recruitment.[3] However, NO is a potent inhibitor of platelets and therefore, if this mechanism was involved, a prothrombotic phenotype in $\alpha 9^{fl/fl}$LysMCre^{+} mice could be expected. Another potential mechanism through which α9β1 could potentiate cell migration is modulation of potassium channel permeability.[4]

Osteopontin is an extracellular matrix protein involved in the pathogenesis of various inflammatory diseases. Osteopontin is one of the ligands for α9β1 that is capable of inducing neutrophil chemotaxis in an α9β1-dependent fashion.[5] It is currently unknown whether osteopontin is directly involved in thrombosis, but it was shown to be a potential biomarker for atherothrombotic ischemic stroke and deep vein thrombosis (DVT).[6,7] Thus, osteopontin could be implicated in neutrophil recruitment and the process of thrombosis, which should be explored in future studies.

Another question to be addressed is the role of α9β1 in venous thrombosis. Both neutrophils and neutrophil extracellular traps (NETs) are critical for DVT.[8] In addition to retaining red blood cells in the thrombus, components of NETs exert a procoagulant effect (nucleosomes) and stimulate platelet aggregation (histones). Consequently, exploring the role of α9β1 in DVT may be a promising line of research.

Dhanesha et al demonstrate that platelets could be activated by cathepsin G released from neutrophils in an α9β1-dependent manner. However, it has also been reported that pharmacologic inhibition or genetic ablation of cathepsin G leads to prolonged tail bleeding time in vivo,[9] whereas findings by Dhanesha et al demonstrate that tail bleeding time remained unchanged. Consequently, another molecule or molecules released by neutrophils might be involved.

Another interesting line of inquiry is the mechanism through which engagement of α9β1 promotes formation of NETs. One of the potential mechanisms could

involve NO because it has been demonstrated that NO induces NETosis by stimulating the release of free radicals.[10] Further studies are needed to clarify whether additional signaling molecules implicated in NET production, such as peptidylarginine deiminase 4 or nicotinamide adenine dinucleotide phosphate oxidase, mediate this effect of α9β1.

In conclusion, the study by Dhanesha et al gives an important insight into understanding the mechanisms of thrombosis. These findings open new horizons for developing novel treatment strategies based on targeting the immune system rather than platelets or clotting factors. Looking forward, this could make thrombosis treatment safer and more efficient.

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LYMPHOID NEOPLASIA

Comment on Al-Sawaf et al, page 866

Venetoclax-obinutuzumab: harnessing complexity

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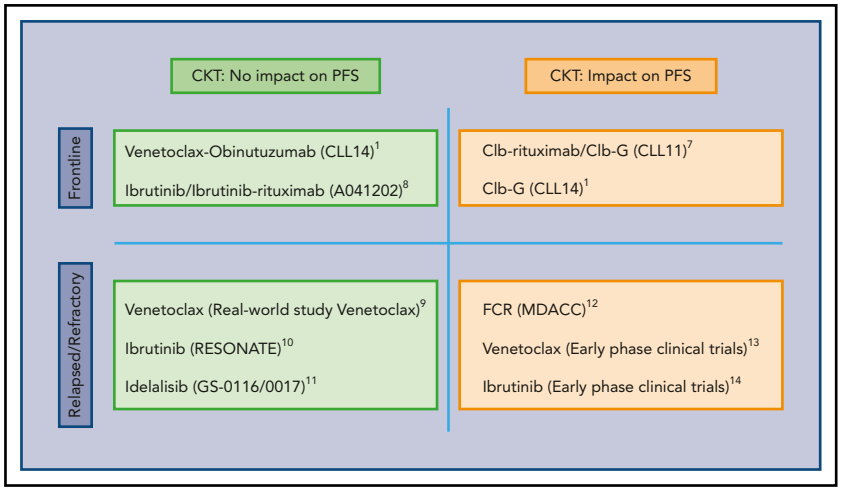
In this issue of *Blood*, Al-Sawaf et al[1] show that a complex karyotype (CKT, defined as 3 or more chromosomal abnormalities in 2 or more metaphases) has predictive value in treatment-naive patients with chronic lymphocytic leukemia (CLL) who received chlorambucil-obinutuzumab (ClbG) in the randomized CLL14 trial,[2] whereas in patients randomized to receive venetoclax-obinutuzumab (VenG), the CKT did not impact the clinical outcome.

Over the past 7 years, therapeutic paradigms for patients with CLL have changed based on the use of clinically validated targeted therapies.[3] However, it is important to evaluate the results of these therapies in known risk groups in CLL, such as those with a CKT.

Expression of the BCL-2 family protein members that tightly regulate the apoptotic process is skewed toward a phenotype aimed to evade apoptosis in CLL.[4] Blocking BCL-2 protein function by the BH3 mimetic drug venetoclax leads to apoptosis of CLL cells and disease control.[5] Recently, VenG was shown to be more active than ClbG in the CLL14 trial. This trial examined initial treatment of CLL patients with comorbidities defined by the presence of a CIRS (Cumulative Illness Rating Scale) >6 and/or creatinine clearance <70 mL/min.[2] Why was this study by Al-Sawaf et al performed? Biological and genetic analyses in most of the trials employing targeted therapies are somewhat limited, making analysis



Influence of CKT on the PFS of CLL patients. The predictive value of CKT in CLL treated with target therapy remains to be established. CKT is associated with shorter PFS in patients treated with chemoimmunotherapy combinations and in many studies of heavily pretreated patients included in early-phase clinical trials. In contrast, the current study suggests that activity of some targeted therapies employed at initial treatment may not be influenced by the presence of CKT. Clb, chlorambucil; FCR, fludarabine, cyclophosphamide, rituximab; G, obinutuzumab.[1,7-14]