inhibitors. The possibility also exists that other mutant oncoproteins implicated in leukemogenesis, and for which specific inhibitors are not yet available, could represent additional targets for this strategy.

There are, however, several questions and caveats that could clearly determine the potential of this approach. For example, it remains to be established whether the ATRA/ATO strategy targets mutant NPM1-expressing leukemia-initiating cells (stem cells) which, at least theoretically, could be responsible for disease relapse. In addition, although both cultured and primary NPM1-mutant AML cells were very susceptible to this regimen, it is less certain whether the degree of cell killing can approximate that observed in the case of APL cells. Finally, although the ATRA/ATO regimen showed some activity in patients with mutant NPM1 AML, it is generally recognized that survival benefits in this (or other) disease(s) absent objective complete responses are unlikely. In this regard, the finding that ATRA/ATO enhanced the activity of an active anti-leukemic agent (eg, daunorubicin) in mutant NPM1 AML is noteworthy and raises the possibility of a more effective future approach. Alternatively, combining the ATRA/ATO strategy with other targeted therapies, including those directed against NPM1 itself, may provide opportunities for cure in this disease, as observed in some patients with APL. Finally, extrapolation of this strategy to other AML subtypes that display different oncogenic mutant proteins represents a promising possibility and one that clearly deserves further investigation.

Conflict-of-interest disclosure: The author declares no competing financial interests.

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THROMBOSIS AND HEMOSTASIS

Comment on Gebhart et al, page 3477

Lupus anticoagulant, thrombosis, and death

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In this issue of Blood, Gebhart et al report a prospective observational cohort study evaluating 151 patients with persistently positive lupus anticoagulant (LA) for a median period of 8.2 years. They observed increased mortality in LA-positive patients, mainly due to new thrombotic events.1

A 32-year-old woman was referred to the hematology clinic after she was found to have persistently positive LA tests. In such a case, 3 distinct scenarios may prompt very different responses by the hematologist. In scenario 1, the patient has no symptoms or signs of antiphospholipid syndrome (APS) other than a positive LA. In scenario 2, she has livedo reticularis and thrombocytopenia that cannot be diagnosed as a definite APS. In scenario 3, she has already been diagnosed with APS due to thrombotic events and/or pregnancy complications. What are the consequences of having a positive LA for this patient? How should the hematologist manage these 3 situations?

Unfortunately, only a few prospective studies have addressed these questions. Antiphospholipid antibodies (aPLAs) are a group of immunoglobulins that can bind to phospholipid-protein complexes. Three major antibody groups (LAs, anticardiolipin antibodies [aCLs], and anti-beta-2-glycoprotein I [anti-beta2GPI] antibodies) are thought to be involved in the pathogenesis of APS and are accepted as being part of the serological criteria for its diagnosis.2 Appropriate laboratory identification of aPLAs is critical because the clinical criteria for APS (thrombosis and recurrent pregnancy complications) are very common. Although the prevalence of aPLAs in healthy populations has been reported to be as high as 5% in some studies,3 these high rates are due to very liberal cutoff definitions. In a large multicenter case-control study, the prevalence of LAs, aCLs, and anti-beta2GPI antibodies in 628 healthy women was found to be 0.63%, 0.96%, and 0.95%, respectively, when the cutoff level was defined as above the 99th percentile of normal.4 All aPLAs are thought to be associated with the clinical findings of APS, but prospective studies have shown both thrombosis and pregnancy morbidity to be more strongly associated with LAs than with aCLs or anti-beta2GPI antibodies.4,5 In a prospective study involving 82 newly diagnosed immune thrombocytopenia patients, 31 patients were found to have aPLAs at the time of diagnosis (as in scenario 2). Fourteen patients in the aPLA-positive group developed thrombosis after 5 years of follow-up, and patients with LAs showed a significantly high risk for thrombosis (relative risk, 7.15).6 Which

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patients in these 2 groups (scenarios 1 and 2) will subsequently experience thrombosis? How can we identify them so as to prevent these thrombotic events? There are still no evidence-based answers for these questions. The general approach for such patients is to eliminate the secondary risk factors for thrombosis, such as obesity and smoking, and recommend antithrombotic prophylaxis in high-risk situations, such as surgery.7 The benefits of low-dose aspirin for primary prevention of thrombosis are still being debated for patients with APS.8 The Euro-Phospholipid Project9 is the biggest prospective study of APS patients, involving 1000 patients with definite APS (as in scenario 3), and has provided important data in terms of the morbidity and mortality of this syndrome. Ninety-three patients (9.3%) died during 10 years of follow-up; the major causes of mortality were thrombosis (36.5% of all deaths), infections (26.9%), and bleeding (10.7%). Survival rates after 5 and 10 years were found to be 94.7% and 90.7%, respectively.

In the present study, Gebhart et al prospectively investigated 151 LA-positive patients for a median of 8 years.1 At the beginning of the study, 39 patients had no clinical findings attributed to an autoimmune disease (as in scenario 1), 112 patients were diagnosed with APS, and 29 patients had concomitant systemic lupus erythematosus (as in scenario 3). Thirty patients (20%) experienced thromboembolic events during follow-up; 14 of them were arterial thrombosis. During the study period, 20 patients (13%) died: 10 of thrombosis, 5 of bleeding, and 5 of other causes. The cumulative relative survival rate after 10 years was 79.7%, which is very low compared with both the matched reference normal population and APS cohorts of the Euro-Phospholipid Project. The authors showed that new onset of thrombosis was the strongest predictor of poor prognosis, associated with a sixfold increase in mortality. A poor survival rate was not associated with the presence of aCLs and anti-β2 GPI antibodies, prior history of thrombosis or pregnancy complications, or prior diagnosis of an autoimmune rheumatic disease in their cohort.1 Furthermore, a new thrombotic event developed under anticoagulant or antplatelet therapy in ~75% of the patients. Interestingly, patients receiving anticoagulant and/or antplatelet therapy showed higher incidences of thrombotic events (23 of 97, 24%) than patients with no therapy (7 of 54, 13%).1 The Euro-Phospholipid Project also showed similar findings.9 There are several possible explanations for why APS patients who were not receiving antithrombotic therapy had lower thrombosis rates. First, patients who were prescribed antithrombotic therapy may have had additional risk factors for thrombosis and may therefore represent a different high-risk group. Second, the results could indicate that current antithrombotic regimens are not effective or sufficient for preventing thrombosis in APS patients. In both Gebhart’s study and the Euro-Phospholipid Project, some patients experienced thrombosis under therapeutic international normalized ratio [INR] values (INR 2–3). Finally, pathologies other than coagulation activation may also contribute to the development of vascular occlusions in some APS patients, including thrombotic microangiopathy, complement activation, and others.

In conclusion, Gebhart et al have clearly shown that the young female patient with LA described above is at increased risk for thrombosis. Our ability to identify higher-risk patients may be improved by better definition of risk factors for thrombosis other than LA and by improved understanding of the unique aspects of the pathophysiology of thrombosis in APS patients.

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Comment on Buchanan et al, page 3484

The first specific antiplatelet antitode

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In this issue of Blood, Buchanan and coauthors present the development of a specific antitode for ticagrelor.1 In fact, this is the first specific antitode against any antplatelet agent.

Ticagrelor is a widely used reversible adenosine 5′-diphosphate (ADP) P2Y12 antagonist for treatment of patients with acute coronary syndrome (ACS). In the Platelet Inhibition and Patient Outcomes trial, ticagrelor reduced the combined end point of death from vascular causes, myocardial infarction, or stroke for up to 12 months, and even reduced total mortality.2 However, patients also experienced increased bleeding events not associated with coronary–artery bypass grafting (CABG). In the recently published Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 trial, patients with a myocardial infarction 1 to 3 years prior to

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