observations question whether additional acquired mutations contribute to the more advanced phenotypes. Indeed, as one example, *ASXL1* lesions have been reported to occur recurrently in one-third of patients with germline GATA2 lesions.[10] Finally, no mutations were recorded in the 82 patients with treatment-related MDS, implying that additional unidentified loci are responsible for conferring a risk of developing this generally fatal secondary late effect.

Although the initial kindreds with MonoMAC syndrome demonstrated an autosomal dominant pattern of inheritance, only 12 of the 53 $GATA2^{mut}$ patients with an available family history were found to have an affected family member in the current study. The lack of family history in the majority of patients highlights the importance of screening children and adolescents for *GATA2* mutations with MDS. *GATA2* mutational status did not affect overall survival, nor were the overall rates of bacterial, viral, fungal, or parasitic infections different among $GATA2^{wt}$ and $GATA2^{mut}$ patients undergoing hematopoietic stem cell transplant. However, identifying affected patients will be essential to predict those who would not benefit long term from supportive care or immunosuppressive therapy and thus be candidates for swift hematopoietic stem cell transplant. Screening affected family members would obviously also be critical for identifying appropriate allogeneic donors.

This important study also raises several important questions about the function of the identified variant alleles. Specifically, noncoding mutations in intron 4 were found in both patients with MDS as well as in nonaffected family members. This was not seen with coding mutations detected in either of the ZF regions. In addition, in distinction to MonoMAC patients who often present with monocytopenia,[3] pediatric patients with $GATA2^{mut}$ MDS frequently had monocytosis, which may or may not be related to the high proportion of coexisting presentation of advanced MDS, monosomy 7, or cooperative genetic events.

Wlodarski and colleagues have made an important contribution to the field of pediatric MDS with these findings. Although primary MDS in children is still considered an idiopathic disorder, *GATA2* should be recognized as a common predisposing factor for the development of primary advanced MDS in childhood and even more so in adolescence. Monitoring for cytogenetic evolution, secondary mutations and signs of advanced disease such as worsening cytopenias will also be important to identify patients in need of swift transplantation. This important paper serves as another reminder of the protean nature of *GATA2*-related disorders and will affect the clinical care of children and adolescents affected with primary MDS.

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● ● ● CLINICAL TRIALS AND OBSERVATIONS

Comment on Martinelli et al, page 1417

Less menorrhagia for women with VTE

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In this issue of *Blood*, Martinelli et al provide reassuring data that women taking oral anticoagulant therapy for venous thromboembolism (VTE) may use estrogen or progestin hormonal therapy to control the menstrual bleeding without increased risk for recurrent thromboembolism.[1]

It is a well-established fact that estrogens increase the risk for VTE twofold to fourfold in a dose-dependent way.[2] The risk is also increased with progestins (synthetic progestogens such as norgestimate, desogestrel, and gestodene) of the third generation compared with those of the first or second generation (eg, ethisterone, norgestrel, and levonorgestrel).[2] Patients who develop VTE while taking oral contraceptives or hormone substitution after menopause are instructed to discontinue this medication. There is controversy regarding whether discontinuation should be immediate upon diagnosis of the thromboembolic event or can be deferred to the time point of discontinuation of anticoagulant therapy. The former recommendation is found in a World Health Organization (WHO) publication from 2010, stating that estrogen-containing oral contraceptives should not be used, even on established oral anticoagulation.[3] The implication is twofold, namely that women on oral anticoagulants that are potentially teratogenic have limitations in their choice of suitable contraceptives and that anticoagulant-associated menorrhagia may be more common when estrogen-containing medication is withheld. Conversely, the Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH) has, in a guidance

document, suggested "hormonal therapy can be continued in selected patients … but anticoagulant therapy should be continued for the duration of hormonal therapy."[4] The reasoning is that the oral anticoagulant effect trumps that of estrogens.

In general, vitamin K antagonists (VKAs) are considered very effective to prevent recurrent VTE, the main exception being in patients with active cancer.[5] The relative risk reduction of well-managed VKAs compared with placebo/control is about 90%.[6] Another way to estimate the high efficacy of oral anticoagulation is with primary prophylaxis in settings with a very high risk of thrombosis. In hip fracture surgery, where the risk of VTE is extremely high due to trauma, surgery, and immobilization in typically elderly patients, VKA compared with no prophylaxis provides 55% relative risk reduction for asymptomatic deep vein thrombosis (DVT) and 80% relative risk reduction for symptomatic pulmonary embolism (PE).[7] The baseline risk of fatal PE after hip fracture surgery is about 4%.[8] In comparison, that risk in women taking oral contraceptives is 0.25 cases (95% confidence interval [CI], 0.16-0.37) per 100 000 treatment years, according to reports to the Medical Products Agency in Sweden.[9] Obviously, this risk will increase among women who already have manifested their propensity by developing a VTE if the trigger is not removed, still remaining far below that of hip fracture surgery.

Martinelli et al have now evaluated the additional risk of continuing hormonal therapy in women younger than 60 years of age with VTE treated with either low-molecular-weight heparin followed by VKA or with rivaroxaban.[1] They used the patient population in the randomized, controlled, open-label design phase 3 trials for DVT or PE. There were 1888 women who could be analyzed, evenly distributed between the 2 anticoagulant regimens. Of those, 475 women were taking concomitant hormonal treatment, either remaining on it despite the VTE diagnosis (n = 402) or initiated during the study period (n = 73). The key finding of this study was the similar incidence density (incidence rate during the time periods at risk) among those on hormonal therapy (3.7% per year) and those off/without hormonal therapy (4.7% per year). After adjustment for age, prior hormonal therapy, assigned anticoagulant treatment, and cancer at baseline, the hazard ratio (HR) for recurrent VTE was 0.56 (95% CI, 0.23-1.39). In addition, there was no difference in crude incidence densities between women taking estrogen only vs progestin only (3.7% per year and 3.8% per year, respectively), suggesting that the patient may continue with the type of hormonal therapy of her choice while on anticoagulation. It is important to note that behind these event rates are only 7 VTE events on hormonal therapy (4 on estrogen-containing and 3 on progestin-only therapy).

Another important finding in this study was the more frequent occurrence of abnormal uterine bleeding, as obtained from patient and investigator reporting of adverse events and bleeding events, with rivaroxaban compared with VKA with an HR of 2.13 (95% CI, 1.57-2.89). In this analysis, the authors made adjustments, in addition to those mentioned above, for anemia at baseline and gynecologic disorders. A recent retrospective study on women of reproductive age and receiving anticoagulant treatment of VTE in clinical practice showed that rivaroxaban prolonged the menstrual bleeding by 1 day and also was associated more frequently than VKA with medical or surgical intervention for menorrhagia (25% vs 7.7%).[10]

These results and observations lead to the following conclusions:

- Oral anticoagulation seems to provide sufficient protection against recurrent VTE to allow for concomitant hormonal therapy if needed.
- Women of reproductive age may suffer from menorrhagia when treated with anticoagulants with a higher risk thereof if rivaroxaban is used. This might also apply to other direct-acting oral anticoagulants. Adequate information regarding this risk should be given to the patient when initiating anticoagulation.
- For women with menorrhagia on anticoagulant therapy, hormonal treatment or tranexamic acid are alternatives to reduce the bleeding. The latter will obviously not provide a contraceptive effect that also may be desired.
- For patients with menorrhagia that is difficult to manage on rivaroxaban, a switch to VKA should be considered.

We can therefore rely on the guidance document from the SSC of the ISTH[4] but one remaining concern is that the thrombogenic effect of estrogens does not disappear precipitously upon discontinuation. The WHO Collaborative Study had noted that the effect disappeared 3 months after stopping oral contraceptives.[2] It therefore seems reasonable to recommend the patient to discontinue oral contraceptives or oral estrogen substitution at least 1 month before planned discontinuation of anticoagulation rather than at the same time.

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