inside blood commentary

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MYELOID NEOPLASIA

Comment on Wlodarski et al, page 1387

Pediatric MDS: GATA screen the germline

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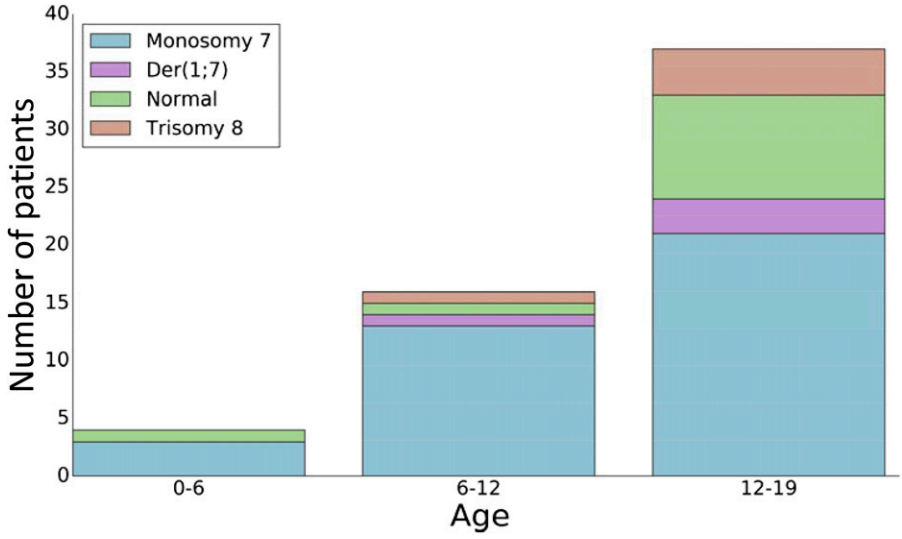
In this issue of *Blood*, Wlodarski and colleagues demonstrate that as many as 72% of adolescents diagnosed with myelodysplastic syndrome (MDS) and monosomy 7 harbor germline mutations in *GATA2*.[1] Although pediatric MDS is a very rare diagnosis, occurring in 0.8 to 4 cases per million,[2] Wlodarski et al screened >600 cases of primary or secondary MDS in children and adolescents who were enrolled in the European Working Group on MDS consortium over a period of 15 years. The overall frequency of germline *GATA2* mutations in children with primary MDS was 7%, and 15% in those presenting with advanced disease. Notably, mutations in *GATA2* were absent in patients with therapy-related MDS or acquired aplastic anemia.

Germline mutations in *GATA2* were previously described in several congenital disorders, including MonoMAC[3] and Emberger syndromes.[4] MonoMAC syndrome is characterized by monocytopenia, frequent opportunistic infections, and a predisposition to developing MDS and acute myeloid leukemia. In 2011, several groups used next-generation sequencing technologies to screen kindreds with MonoMAC syndrome, identifying heterozygous germline mutations in *GATA2*, predominantly affecting the zinc finger (ZF) regions of this essential hematopoietic and endothelial transcription factor.[3,5,6] Subsequently, germline *GATA2* mutations were found to cause certain forms of congenital neutropenia as well as Emberger syndrome, which is characterized by lymphedema and a predisposition to MDS/acute myeloid leukemia.[4] Although the majority of mutations occur in the coding region of the ZF1 and ZF2 domains, Wlodarski et al also describe recurrent noncoding mutations in the +9.5kb regulatory intronic region of *GATA2* upstream of exon 4.



Presenting age and karyotypic features of patients with MDS and germline *GATA2* mutations, Wlodarski et al report that patients with primary MDS and germline *GATA2* mutations are likely to be older at diagnosis and have monosomy 7 compared with patients without *GATA2* mutations. The figure has been adapted from Figure 2 in the article by Wlodarski et al that begins on page 1387.

GATA2 is an essential zinc finger transcription factor that is critical for early developmental hematopoiesis. *Gata2*$^{-/-}$ mice die at E10.5 because of lack of early hematopoiesis,[7] and conditional knockout mice also die later in gestation of edema and hemorrhage because of failure of fetal liver hematopoiesis and defective lymphatic development.[8] There is broad evidence that haploinsufficiency of *GATA2* leads to a loss of hematopoietic stem cells, and in humans, preferentially leads to depletion of dendritic, monocyte, B, and natural killer cells.[3,4,6] Rarely, gain-of-function *GATA2* mutations have also been described as secondary events in certain cases of blast crisis chronic myelogenous leukemia.[9]

In screening this large cohort of children and adolescents with primary and secondary MDS, Wlodarski et al reveal a number of interesting findings that lead to further questions. First, the incidence of *GATA2* mutations was significantly higher in those with advanced MDS (15%, 13/85) compared with lower-grade MDS (4%, 15/341) ($P < .01$). Strikingly, 70% of patients with *GATA2* mutations had monosomy 7 vs only 11% without ($P < .01$). Second, patients with *GATA2* mutations were also older at diagnosis compared with those without (median age, 12.3 vs 10.3 years) ($P < .01$). Together, these

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.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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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