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CLINICAL TRIALS AND OBSERVATIONS

Comment on Stock et al, page 1548

Should young adults with ALL be treated as children?

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In this issue of *Blood*, Stock et al report the results of a large multicenter phase 2 study that evaluated the use of a pediatric chemotherapy regimen to treat older adolescents and young adults (AYAs) with acute lymphoblastic leukemia (ALL).[1]

This Cancer and Leukemia Group B (CALGB) 10403 (Alliance) trial enrolled 295 evaluable patients age 16 to 39 years with Philadelphia chromosome–negative (Ph^-) ALL. The CALGB 10403 trial used the same chemotherapy regimen as that used in one of the arms for children with high-risk ALL in the randomized Children's Oncology Group (COG) AALL0232 protocol.[2] More precisely, the treatment used in this AYA trial was the same as the prednisone-Capizzi methotrexate treatment used for rapid early responders in the original COG protocol. Interestingly, because pediatric indications for allogeneic stem cell transplantation (SCT) in first complete remission (CR1) were retained, only 20 of the 263 patients who achieved a CR received allogeneic SCT in CR1. Consequently, the very good 59% (95% confidence interval [CI], 54%-65%) event-free survival and 73% (95% CI, 68%-78%) overall survival estimates at 3 years essentially reflect the effects of chemotherapy.

At the end of the twentieth century, it was generally accepted that the outcomes of adult ALL would remain markedly and indefinitely worse than those of childhood ALL. This was thought to be mostly a result of the lower incidence of good-risk ALL subsets and the higher incidence of high-risk ALL subsets in adults compared with children, a fact that has been documented more often in B-lineage cases.[3] Between 2003 and 2008, 6 retrospective analyses from 6 different countries reported much better outcomes when using pediatric vs adult regimens in narrow age ranges of patients (ranging from 14 to 20 years old). It became evident that differences in biology might not explain everything and that differences in therapy might matter.[4]

Cooperative groups for adult patients with ALL then decided either to adapt pediatric regimen protocols by introducing their key components (as was done in the so-called pediatric-inspired protocols from the German Multicenter Study Group for Adult ALL, Italian Northern Italy Leukemia Group, French-Belgium-Swiss Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL), and Spanish Programa Español de Tratamientos en Hematología groups) or to simply use an unmodified pediatric regimen (as in UKALL-2003,[5] Nordic Group ALL2008,[6] or CALGB 10403). The main differences between these 2 strategies were the upper age limit for eligibility, which was lower in trials using unmodified pediatric regimens (age 24-45 years) than in pediatric-inspired trials (age 55-65 years) and the rate of receipt of allogeneic SCT in CR1, which was usually higher in pediatric-inspired trials.

To date, the lack of randomized trials and the variability in all these regimens make it very difficult to determine which of these 2 strategies should be recommended. Likewise, we do not know what the upper age limit should be for AYAs treated with an unmodified pediatric protocol rather than a modern pediatric-inspired protocol. There are variations in treatment intensity in both adult and pediatric chemotherapy regimens. The word "pediatric" does not always mean chemotherapy of greater intensity. In this respect, one questions whether some patients treated in the CALGB 10403 study would have benefited from a more intensive regimen. The COG AALL0232 protocol included more intensive treatment arms for slow early responders. In the CALGB 10403 study, the therapy designed for rapid early responders was used in all patients, probably for safety concerns. Early minimal residual disease levels were not prospectively used for treatment intensification or allogeneic SCT indication in CR1, as is currently done in most European ALL protocols.

There is also uncertainty regarding the upper age limit for adults for using intensive pediatric or pediatric-inspired chemotherapy regimens that maintain treatment intensity with acceptable toxicity. This issue was retrospectively addressed in the GRAALL-2005 trial, in which the upper age limit was determined to be 54 years.[7] Again, several factors may have had an impact on this age determination, including chemotherapy intensity, the rate of allogeneic SCT, the number of participating centers, and the learning curve for centers learning to administer complex multidrug and multiphase protocols.

In summary, the article by Stock et al confirms the value of intensifying chemotherapy in AYAs with Ph^- ALL. Stock et al note that the first-line introduction of antibody-based therapy in B-cell precursor ALL patients, kinase inhibitors in Ph-like ALL patients, and nelarabine in T-cell ALL patients provides exciting new opportunities for improving the outcome of adult ALL. Paradoxically, this might lead to a selective reduction of intensity as new combinations of chemotherapy and new agents are studied, as was the case with Ph^+ ALL when tyrosine kinase inhibitors were introduced.[8]

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

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VASCULAR BIOLOGY

Comment on Lafiti et al, page 1597

Ponatinib and platelets a conflict in CML

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In this issue of *Blood*, Lafiti et al address the critical question of vascular and cardiac toxicity of ponatinib, using a mouse model.[1] They elegantly show that ponatinib vascular toxicity is due to von Willebrand factor (VWF)-mediated platelet adhesion.

Ponatinib, a third-generation tyrosine kinase inhibitor (TKI), has been approved for the treatment of TKI-resistant or -intolerant chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph^+ ALL). Although ponatinib has a powerful effect on T315I-mutated cells, cardiovascular, cerebrovascular, and peripheral vascular thrombosis, including fatal myocardial infarction and stroke, have occurred in ponatinib-treated patients. In clinical trials, serious arterial thrombosis and venous thromboembolism occurred in at least 35% and 6% of ponatinib-treated patients, respectively. Heart failure, including fatal cases, occurred in 9% of ponatinib-treated patients.[2]

To explore the vascular toxicity due to endothelial alterations from ponatinib, Lafiti et al used in vivo ultrasound molecular imaging and intravital microscopy. The animal models included a wild-type C57Bl/6 mouse and a hyperlipidemic mouse harboring the apoliprotein-E gene deletion (ie, $ApoE^{-/-}$ mice). They compared ponatinib to dasatinib treatment in these 2 mice strains. Dasatinib was selected as a control because this TKI was known to induce very few thrombotic events. Mice were also treated with *N*-acetylcysteine (NAC), which reduces VWF multimer size or recombinant human ADAMTS13, a regulatory protease that cleaves ultralarge VWF. A large panel of in vivo imaging methods was employed to investigate the endothelial angiopathy. Mice were the unfortunate actors in movies performed with contrast-enhanced ultrasound molecular imaging, intravital microscopy, echocardiography, or computed tomography coronary angiography. I really encourage the readers to look at the impressive videos provided in the supplemental data. The treatment-related mortality was significantly higher in ponatinib-treated mice. As has been observed in patients, blood pressure measurements in animals acclimatized to the procedure revealed a gradual increase in both systolic and diastolic blood pressure in ponatinib-treated wild-type and $ApoE^{-/-}$ mice. This supports the previous observation of the activity of ponatinib on vascular endothelial growth factor receptor-2.

In both large arteries and the peripheral microcirculation, ponatinib caused a prothrombotic angiopathy. More precisely, ponatinib increased endothelial VWF with exposure of the A1 binding domain, and platelet adhesion several fold within days of the onset of treatment. The use of a high dose of rADAMTS13 reversed aortic platelet adhesion in ponatinib-treated mice. Thus, ponatinib caused an acquired resistance to VWF. Treatment of $ApoE^{-/-}$ mice with NAC, coadministered daily with ponatinib, also eliminated the VWF signal but reduced the platelet signal only by half. Of interest, there was no coronary artery occlusion or stenosis but rather wall motion abnormalities as revealed by left ventricular coronary microvascular anatomy. In the aggregate, these data provided evidence of a thrombotic microangiopathy due to ponatinib. This is consistent with postmortem findings in patients of coronary microvascular thrombosis and histologic evidence of platelets adhesion.

Ponatinib also increased surface expression of VWF on human umbilical vein endothelial cells (HUVECs) cultured in a microfluidic system, indicating that increased surface mobilization and decreased proteolytic cleavage played a role in the angiopathy. Ponatinib inhibited HUVEC tube formation, indicating a possible suppressive effect on neoangiogenesis of vascular endothelial cells.[3] Using transgenic zebrafish lines, it has been shown that ponatinib inhibits cardiac survival signaling pathways, leading to cardiomyocyte apoptosis and ventricular dysfunction.[4]

The activity of ponatinib on coagulation has also been studied. Gene expression and pathway analysis demonstrated that ponatinib enhanced the messenger RNA expression of coagulation factors of both the contact activation (intrinsic) and the tissue factor (extrinsic) pathways. In line