To the editor:

Thiopurine methyltransferase in acute lymphoblastic leukemia

We recently reported that specific genetic polymorphisms, particularly polymorphisms in thymidylate synthase (TYMS) and glutathione S-transferase M1 (GSTM1) predicted the risk of relapse among children with acute lymphoblastic leukemia (ALL). An accompanying commentary noted surprise that the thiopurine methyltransferase (TPMT) genotype was not predictive of relapse risk. The answer may lie in the fact that the starting dose of mercaptopurine (75 mg/m² per day) in our study was higher than a lower dose of mercaptopurine than we used (60 mg/m² per day), status and then prescribed doses of mercaptopurine that are tailored to their TPMT genotype or phenotype. At St Jude Children’s Research Hospital, since the early 1990s, we have used a combination of measurement of thiopurine metabolites, TPMT status, and clinical tolerance to continuation therapy to selectively decrease the dose of mercaptopurine (without decreasing the nonthiopurine therapy) in patients with low or intermediate TPMT activity, to counsel patients on compliance if thiopurine metabolites are low, and to increase doses of chemotherapy in patients demonstrating persistently high white blood cell counts. Because we have previously found that constant administration (ie, avoiding interruption) in thiopurine therapy resulted in fewer relapses, our goal has been to maintain the highest dose of daily mercaptopurine that is tolerable. Using this approach, TPMT genotype was not predictive of hematologic relapse risk in our study Total XIIIB (Figure 1), with 5-year cumulative incidences of 13.2% ± 2.3 versus 6.7% ± 6.7% among patients with the wild-type versus low-activity genotypes, respectively ($P = .46$).

As Zwann indicated, after 2 weeks of including a somewhat lower dose of mercaptopurine than we used (60 mg/m² per day),
patients with deficient or heterozygous *TPMT* genotype in a front-line BFM trial in ALL had a lower level of minimal residual disease than those with wild-type *TPMT*. Whether a similar relationship between *TPMT* genotype and ultimate relapse risk will be observed over the longer term, in the context of multiagent chemotherapy that involves higher doses of mercaptopurine as well as other agents, remains to be seen, and will likely be influenced by the strategies used for dosage adjustment during continuation therapy.

Our finding that long-term outcome was not related to TPMT status, in a setting in which dosages were individualized based partly on each patient’s TPMT status, is evidence that pharmacogenetic dosage individualization strategies can be used to mitigate toxicity without compromising efficacy.

Mary V. Relling, Ching-Hon Pui, Cheng Cheng, and William E. Evans

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**To the editor:**

**Lack of *IKBA* coding region mutations in primary mediastinal large B-cell lymphoma and the host response subtype of diffuse large B-cell lymphoma**

The role of inhibitor of kappa Bα (*IKBA*) mutations in lymphoid malignancies with constitutive NF-κB signaling remains to be defined. We recently characterized the molecular signatures of primary mediastinal large B-cell lymphoma (MLBCL) and 3 subtypes of diffuse large B-cell lymphoma (DLBCL). The primary MLBCL signature had striking similarities to that of classic Hodgkin lymphoma (cHL), a clinically related disorder. Like cHL, primary MLBCL exhibited nuclear localization of the c-REL subunit of NF-κB and increased expression of multiple NF-κB target genes. In addition, MLBCL cells transduced with an *IkBa* superrepressor exhibited markedly decreased NF-κB activity and significantly increased apoptosis, confirming the role of *IkBa* and the NF-κB pathway in MLBCL cell survival. Of interest, the newly identified host response (HR) subtype of DLBCL also had significantly increased coordinate expression of multiple NF-κB target genes, implicating the NF-κB survival pathway in this additional subtype of LBCL.

Previous studies suggest that DLBCLs that share features with normal in vitro activated B cells (“ABC-like” tumors) also exhibit NF-κB activation and express a more restricted set of NF-κB target genes. In addition, “ABC-like” DLBCL cells transduced with an *IkBa* superrepressor had markedly decreased tumor cell survival.

In earlier analyses of potential genetic bases for constitutive NF-κB activation in lymphoid malignancies, somatic mutations of *IKBA* were described in a subset of cHL. In contrast, *IKBA* mutations were rare in a recently described small series of “ABC-like” DLBCLs. *IKBA* mutations were not found in 9 of 10 of such differentiation-associated DLBCLs; a single tumor had both a somatically mutated and wild-type copy of *IKBA*.

To determine whether *IKBA* mutations were present in primary MLBCLs or HR DLBCLs, we subjected 26 MLBCL and 16 HR DLBCL RNAs to reverse-transcriptase–polymerase chain reaction (RT-PCR) of the entire coding region of *IKBA* cDNA and sequenced the resulting *IKBA* PCR products. Only 2 single nucleotide changes were identified in the *IKBA* coding region (bp 95-1048). *IkBa* superrepressor exhibited markedly decreased NF-κB activity and significantly increased apoptosis, confirming the role of *IkBa* and the NF-κB pathway in MLBCL cell survival. Of interest, the newly identified host response (HR) subtype of DLBCL also had significantly increased coordinate expression of multiple NF-κB target genes, implicating the NF-κB survival pathway in this additional subtype of LBCL.

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**References**

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