To the editor:

Thiopurine methyltransferase in acute lymphoblastic leukemia

We recently reported that specific genetic polymorphisms, particularly polymorphisms in thymidylate synthase (TMS) and glutathione S-transferase M1 (GSTM1) predicted the risk of relapse among children with acute lymphoblastic leukemia (ALL). \(^1\) An accompanying commentary noted surprise that the thiopurine methyltransferase (TPMT) genotype was not predictive of relapse risk. \(^2\) The answer may lie in the fact that the starting dose of mercaptopurine (75 mg/m\(^2\) per day) in our study was higher than some groups use, and that therapy was individualized based on TPMT status.

TPMT methylates and inactivates mercaptopurine. The approximately 10% of populations that inherit intermediate or absent TPMT activity is at higher risk of myelosuppression and its attendant toxicity if prescribed “normal” doses of thiopurines; \(^3\) in addition, such patients appear at higher risk of secondary cancers. \(^4\) TPMT activity is inherited as a monogenic autosomal codominant trait, with the vast majority of inactivating alleles accounted for by single nucleotide polymorphisms at amino acids 238, 460, and 719. \(^5\) TPMT activity can also be measured directly in erythrocytes. \(^6\) Thus, patients can be clinically screened for TPMT status and then prescribed doses of mercaptopurine that are tailored to their TPMT genotype or phenotype. \(^6\) 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, \(^9\) 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 XIIIIB (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/m\(^2\) 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.\(^\text{10}\) 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 mercaptourine 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

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 B\(_\alpha\) (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).\(^\text{1,2}\) The primary MLBCL signature had striking similarities to that of classic Hodgkin lymphoma (cHL), a clinically related disorder.\(^\text{1,3}\) Like cHL, primary MLBCL exhibited nuclear localization of the c-REL subunit of NF-κB and increased expression of multiple NF-κB target genes.\(^\text{1,4}\) In addition, MLBCL cells transduced with an IκB\(_\alpha\) superrepressor exhibited markedly decreased NF-κB activity and significantly increased apoptosis, confirming the role of IκB\(_\alpha\) and the NF-κB pathway in MLBCL cell survival.\(^\text{4}\) 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.\(^\text{2,4}\)

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.\(^\text{4,5}\) In addition, “ABC-like” DLBCL cells transduced with an IκB\(_\alpha\) superrepressor had markedly decreased tumor cell survival.\(^\text{5}\)

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.\(^\text{6-8}\) In contrast, IKBA mutations were rare in a recently described small series of “ABC-like” DLBCLs.\(^\text{9}\) 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.\(^\text{9}\)

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 in the IKBA coding region (bp 95-1048) were identified (C to T, position 175; and C to T, position 400); neither nucleotide change altered the IKBA coding sequence.\(^\text{10}\) Both of the identified single nucleotide changes are recognized IKBA single nucleotide polymorphisms (SNPs; SNP IDs: rs1957106 and rs10782383) (http://www.ncbi.nlm.nih.gov/SNP). The polymorphism at position 175 was detected in 7 of 16 HR tumors, 2 of which were homozygous (T/T), and 12 of 26 MLBCLs, all of which were heterozygous (T/C). The polymorphism at position 400 was detected in 16 of 16 HR tumors, 7 of which were homozygous (C/C), and 25 of 26 MLBCLs, 16 of which were C/C. To exclude the possibility that infiltrating normal cells in primary MLBCLs and HR DLBCLs reduced the sensitivity of the assay, we identified the previously described IKBA mutation in L428 lymphoma cells\(^\text{8}\) using L428 RNA admixed with 4-fold higher concentrations of RNA from a cell line with wild-type IKBA (DHL6).

References

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