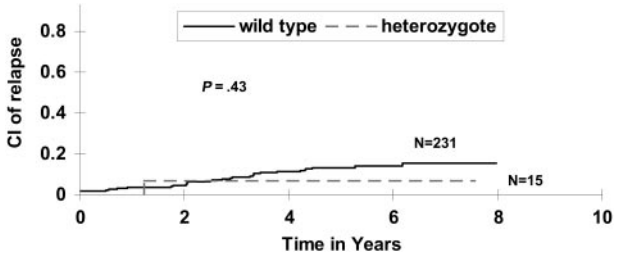

Figure 1. SJCRH protocol total XIIIB: cumulative incidence of relapse. Cumulative incidence of relapse is not higher among TPMT heterozygotes than wild-type patients, adjusting dose of 6MP down among heterozygotes with prospective TPMT assessment.

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*.[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 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

Correspondence: Mary V. Relling, St Jude Children's Research Hospital, 332 N Lauderdale, Rm D1052, Memphis, TN 38105.

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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).[1,2] The primary MLBCL signature had striking similarities to that of classic Hodgkin lymphoma (cHL), a clinically related disorder.[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.[1,4] In addition, MLBCL cells transduced with an IκBα superrepressor exhibited markedly decreased NF-κB activity and significantly increased apoptosis, confirming the role of IκBα and the NF-κB pathway in MLBCL cell survival.[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.[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.[4,5] In addition, "ABC-like" DLBCL cells transduced with an IκBα superrepressor had markedly decreased tumor cell survival.[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.[6-8] In contrast, *IKBA* mutations were rare in a recently described small series of "ABC-like" DLBCLs.[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*.[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.[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[8] using L428 RNA admixed with 4-fold higher concentrations of RNA from a cell line with wild-type *IKBA* (DHL6).

Taken together, our data and that of Thomas et al[9] indicate that mutations of *IKBA* are largely absent in LBCL subtypes, including MLBCL, HR DLBCL, and the differentiation-associated "ABC-like" DLBCLs. These results suggest that alternative mechanisms are likely responsible for the constitutive activation of NF-κB in these tumors.

Hidenobu Takahashi, Friedrich Feuerhake, Stefano Monti, Jeffery L. Kutok, Jon C. Aster, and Margaret A. Shipp

Correspondence: Margaret A. Shipp, Dept of Medical Oncology, Dana-Farber Cancer Institute, 44 Binney St, Boston, MA 02115; e-mail: margaret_shipp@dfci.harvard.edu.

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