Response

Conflicting data on the prognostic significance of FLT3-TKD mutations in cytogenetically normal acute myeloid leukemia (CN-AML) might be related to many factors, including techniques used to detect FLT3-TKD, differences in patient populations studied, and treatment regimens

We appreciate the comments of Mead et al regarding our recent article, and agree it is important to discern the reason(s) for the apparent differences in outcomes of patients with cytogenetically normal acute myeloid leukemia (CN-AML) and point mutations in the FLT3-tyrosine kinase domain (TKD) between the Medical Research Council (MRC) and Cancer and Leukemia Group B (CALGB) studies.

First, although Mead et al analyzed 1007 patients, only 226 of them had CN-AML without FLT3-internal tandem duplication (ITD), including 38 with FLT3-TKD. Therefore, the numbers of CN-AML patients analyzed in both studies were comparable, suggesting that sample size is likely not the main reason for the outcome differences.

Second, we believe that the issue of whether differences in mutant levels can explain outcome differences between studies is difficult to resolve conclusively. In our study, FLT3-TKD patients with apparent 100% of mutant alleles were common, whereas no MRC CN-AML patient with FLT3-TKD had a mutant level above 60%. This discrepancy could be caused by differences in techniques used (a “technical issue”) or distinct biologic features of patients included (a “sampling difference”). We reanalyzed our FLT3-TKD samples increasing sensitivity of wild-type FLT3 allele detection. The median FLT3-TKD percentage for all 14 patients was 74% (range, 14%-94%), while it was 87.5% (range, 74%-94%) among 8 patients initially reported to have 100% of FLT3-TKD alleles. Thus, most patients (93%) remained in the high FLT3-TKD percentage group as defined by Mead et al, suggesting a “sampling difference” between the studies. Notably, we tested only for mutations altering the normal EcoRV restriction site in codons for D835/I836, the most common site of FLT3-TKD. Unlike Mead et al, we did not analyze mutations outside this region. Whether inclusion of these different mutations influenced the outcome results is unknown. To exclude the potential “technical issues,” an exchange of samples for interlaboratory development and validation of standardized assays could be carried out. Meanwhile, we will perform SNP analysis to assess the frequency of biallelic disease as suggested.

Third, the differences in clinical outcome could also stem from differences in patient inclusion criteria and treatment regimens between the CALGB and MRC trials. CALGB 9621 and 19808 enrolled exclusively patients aged between 18 and 59 years with de novo AML, while the MRC studies allowed both younger and older patients, and those with secondary disease. All CALGB patients received induction with cytarabine, daunorubicin, and etoposide with or without the MDR1 inhibitor Valspodar, and approximately 75% of our FLT3-TKD patients received autologous transplantation during first remission. The treatment in the MRC AML 10 and 12 trials was more varied; among 127 FLT3-TKD patients with various karyotypes in the Mead et al study, 14 (11%) received an autograft and 17 (13%) an allograft. The exact numbers of CN-AML patients with FLT3-TKD receiving allograft, autograft or chemotherapy in the MRC study were not reported.

Finally, we believe we were cautious in our suggestion that “CN-AML patients with FLT3-TKD may benefit from more aggressive postinduction therapies” by indicating that the results from “large phase 3 clinical trials . . . [are] likely to provide additional insights.” Although the prognostic significance of FLT3-TKD has not been conclusively established, laboratory data indicate that FLT3-TKD plays an important role in leukemogenesis, thus constituting a potential therapeutic target. This will soon be tested by CALGB 10603, an international study randomizing patients with FLT3-ITD and/or FLT3-TKD to therapy with or without the tyrosine kinase inhibitor midostaurin (Novartis, Basel, Switzerland).

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References


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