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FLT3-ITD signals bad news for core binding factor acute myeloid leukemia unless trisomy 22 comes to the rescue

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Structural rearrangements resulting in either t(8;21)(q22;q22) [RUNX1-RUNX1T1] or inv(16)(p13q22)/t(16;16)(p13.1;q22) [CBFB-MYH11] are pathognomonic for core binding factor (CBF) acute myeloid leukemia (AML). Prognostic classifications have consistently positioned CBF AML as a favorable entity, particularly if the patient can tolerate conventional induction and consolidation chemotherapy. Optimal outcomes for patients with CBF disease are achieved through incorporation of gemtuzumab ozogamicin into 7+3 based induction and high-dose cytarabine into the consolidation phase of therapy.1, 2

Recent molecular studies have highlighted striking differences in the genomic landscape between the two forms of CBF AML. Although kinase activating mutations are observed frequently in both groups, RUNX1-RUNX1T1 more commonly harbors mutations in ASXL1 (14%), ASXL2 (14%), TET2 (11%), RAD21 (11%) and ZBTB7A (19%), whereas CBFB-MYH11 AML is more frequently associated with WT1 mutation (10%). At the cytogenetic level, t(8;21) is more closely linked to del (9q) or loss of a sex chromosome, whereas inv(16) may occur in the company of del(7q) and trisomy 22 abnormalities.3-5

In terms of prognosis, although there is general agreement that additional cytogenetic abnormalities do not consistently increase the risk of relapse in CBF AML, the role of kinase activating mutations has been more controversial.6 The predominant kinase activating mutations in CBF AML involve RAS (27%), KIT (26%) and FLT3 (17%).5 Presence of mutant RAS is generally associated with favorable prognosis in CBF AML.5 In contrast, several series suggest that KIT, in particular exon 17 mutations are associated with increased relapse risk among patients with RUNX1-RUNX1T1, whereas prognostic concordance is lacking for CBFB-MYH11 AML.7, 8

The current paper by Kayser and colleagues9 is a multi-institutional retrospective cohort analysis to address the role of FLT3-ITD co-mutation in CBF AML. The study included 97 patients with similar proportions of t(8;21)(q22;q22) and inv(16)(p13q22)/t(16;16)(p13.1;q22). Most were treated intensively, resulting in a very high complete remission (CR) rate of 98%, despite the presence of FLT3-ITD, with only 3 patients receiving concomitant FLT3 inhibitor. Allogeneic hematopoietic cell transplant (allo-HCT) was performed in 14% of the patient population in first complete remission (CR1). Among patients not transplanted in CR1, almost 40% relapsed with subsequent allo-HCT performed
in ~39% of this group. In this analysis of patients with FLT3-ITD CBF AML, the authors found that allo-HCT was only beneficial for patients at relapse, whereas outcomes were not improved by allo-HCT in CR1. If allo-HCT was not performed at relapse, there were no long-term survivors. Long-term survival was also absent for the small group of patients treated non-intensively. These results prompted the authors to conclude that patients with FLT3-ITD CBF AML should be given intensive induction and consolidation therapy, where possible, and to reserve allo-HCT as a second complete remission (CR2) strategy in the event of relapse after first line therapy. A major caveat is the retrospective nature of the study, which introduces the risk of potential bias. Only 39% of relapsing patients were transplanted, suggesting that the opportunity for cure was lost for the majority of those failing primary therapy. The failure to observe enhanced outcomes for those treated in CR1, however, suggests that not all patients with FLT3-ITD CBF AML have poor prognosis and that heterogeneity in survival must exist.

In search of genetic factors bifurcating prognosis in CBF AML, Kayser et al identified an association between inv(16) and trisomy 22 in 23% cases. Although prior studies have already reported favorable outcome for this chromosomal duet\textsuperscript{10}, the current study extends this finding to patients with trisomy 22, inv(16) and FLT3-ITD mutation. For patients with this molecular triad, relapse-free survival at 4 years was 80%, compared to only 38% for other patients. The authors conclude that patients with CBF and FLT3-ITD with inv(16) and trisomy 22 should be classified as favorable-risk, the remainder as poor risk. It remains uncertain, however, whether outcomes would be improved by upfront allo-HCT in CR1 or whether transplant at relapse would suffice for this poor risk CBF sub-group with FLT3-ITD. Another intriguing question is what candidate genes are carried on chromosome 22, which when amplified by just one copy, can result in dramatic enhancement of prognosis in patients with FLT3-ITD CBF AML.

A major limitation of the paper was the absence of flow or molecular MRD correlation with these prognostic observations. Favorable prognosis in CBF AML is strengthened by multi-log reduction or eradication of measurable residual disease (MRD) after commencing treatment. Despite an admirable effort to refine prognostic outcomes in FLT3-ITD CBF AML, a recurring question is whether the importance of baseline prognostic risk stratification is diminished by dynamic assessment of post-treatment MRD. Although current European LeukemiaNET guidance recommends post-treatment MRD monitoring every 3 months, several studies suggest the window of opportunity to intervene between initial detection of MRD progression by reverse-transcriptase quantitative polymerase chain reaction (RT-qPCR) and clinical relapse is too narrow, making it logistically difficult to orchestrate a meaningful therapeutic intervention.\textsuperscript{12-14} Increasing the intensity of MRD monitoring with more frequent peripheral blood surveillance e.g. monthly for the first 12 months when relapse risk is highest, could permit earlier detection of rising MRD. It remains to be proven whether overall survival would be enhanced by earlier, pre-emptive intervention, as opposed to salvage at the time of morphologic progression. With allo-HCT in CR2 the main priority for patients with relapsing disease, it is likely that early detection and treatment to suppress rising MRD could enhance the proportion of patients bridged to transplant in remission and negative for MRD. Alternatively, it remains an open question whether outcomes will be improved by a pre-transplant MRD reduction strategy, or whether equivalent outcomes could be achieved by proceeding directly to transplant, especially if myeloablative conditioning is planned. The median time to relapse from detection of MRD failure to clinical relapse is only ~3-4 months.\textsuperscript{12} Therefore, a pre-emptive MRD suppression strategy could buy the treating team more time, keeping the patient in remission and free from relapse until the allo-HCT
can be organized and carried out.

In terms of targeting FLT3 to improve clinical outcome in FLT3-ITD CBF AML, treatment could be introduced at either the induction/consolidation stage, during maintenance, preemptively at the time of MRD progression, at morphologic relapse, or as maintenance therapy in the post-allo-HCT setting. Unfortunately, robust data to answer any of these questions is lacking, with FLT3-ITD CBF comprising only ~2% of the AML population, making randomized trial data with any new or future agent or combination within this orphan sub-population an unlikely prospect. The RATIFY trial, which examined the role of midostaurin during induction, consolidation and maintenance in patients with FLT3 mutant AML, only enrolled 16 patients (4%) with CBF AML to the midostaurin arm. In the SORAML trial, the FLT3 inhibitor sorafenib was combined with standard induction and consolidation therapy and as maintenance for 12 months. In the favorable cytogenetic risk group, which comprised only 10% of the study population, sorafenib was associated with improved event-free, relapse free and overall survival in a post-hoc sub-group analysis. The outcomes of patients with FLT3-ITD within this CBF sub-group, however, were not defined.

In summary, as the genomic age continues to reveal further prognostic heterogeneity within conventional AML sub-groups, we will increasingly be challenged with when to pull the trigger on the use of allo-HCT and when to use a growing number of newly approved AML drugs, such as FLT3 inhibitors and so forth, for uncommon clinical scenarios for which definitive randomized evidence may never become available. The current work by Kayser et al. adds to the growing list of AML scenarios where the presence of FLT3-ITD represents bad news, including among patients with CBF AML. Physicians are likely to formulate a logic circuit that suggests that a) it makes sense to use a FLT3 inhibitor to target FLT3-ITD when detected in CBF AML, b) patients with concurrent trisomy 22 should not be candidates for allo-HCT in CR1, c) close monitoring of MRD, potentially with RT-qPCR performed monthly on blood for at least the first 12 months is warranted and d) allo-HCT should be ready to action early if MRD progression is confirmed.

References