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] The presence of mutant *RAS* is generally associated with a favorable prognosis in CBF AML.[5] In contrast, several series suggest that *KIT* mutations, 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 paper published by Kayser and colleagues[9] in this issue of *Haematologica* is a multi-institutional retrospective cohort analysis addressing the role of *FLT3*-internal tandem duplication (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 rate of 98%, despite the presence of *FLT3*-ITD, with only three patients receiving concomitant FLT3 inhibitor. Allogeneic hematopoietic cell transplant (HCT) was performed in 14% of the patient population in first complete remission. Among patients not transplanted in first complete remission, almost 40% relapsed with subsequent allogeneic HCT performed in ~39% of this group. In this analysis of patients with *FLT3*-ITD CBF AML, the authors found that allogeneic HCT was only beneficial for patients at relapse, whereas outcomes were not improved by allogeneic HCT in first complete remission. If allogeneic 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, when possible, and to reserve allogeneic HCT as a strategy in second complete remission 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 in whom primary therapy failed. The failure to observe enhanced outcomes for those treated in first complete remission, however, suggests that not all patients with *FLT3*-ITD CBF AML have a poor prognosis and that heterogeneity in survival must exist.

In search of genetic factors differentiating prognosis in CBF AML, Kayser *et al.* identified an association between inv(16) and trisomy 22 in 23% of cases. Although prior studies have already reported favorable outcome for this chromosomal duet,[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 allogeneic HCT in first complete remission or whether transplant at relapse would suffice for this poor-risk CBF subgroup 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 study was the absence of flow or molecular measurable residual disease (MRD) correlation with these prognostic observations. Favorable prognosis in CBF AML is strengthened by multi-log reduction or eradication of 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 that 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.[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 enable 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 morphological progression. With allogeneic HCT in second complete remission the main priority for patients with relapsing disease, it is likely that early detection and treatment to suppress rising MRD could increase 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 transplantation, especially if myeloablative conditioning is planned. The median time to relapse from detection of MRD failure to clinical relapse is only about 3-4 months.[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 allogeneic 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 the induction/consolidation stage, during maintenance, pre-emptively at the time of MRD progression, at morphological relapse, or as maintenance therapy in the post-allogeneic HCT setting. Unfortunately, robust data to answer any of these questions are lacking, with patients harboring *FLT3*-ITD CBF accounting for only ~2% of the AML population, making randomized trial data with any new or future agent or combinations 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.[15] In the SORAML trial, the FLT3 inhibitor sorafenib was combined with standard induction and consolidation therapy and as maintenance for 12 months.[16] In the favorable cytogenetic risk group, which formed only 10% of the study population, sorafenib was associated with improved event-free, relapse-free and overall survival in a post-hoc subgroup analysis. The outcomes of patients with *FLT3*-ITD within this CBF subgroup were, however, not defined.

In summary, as the genomic age continues to reveal further prognostic heterogeneity within conventional AML subgroups, we will increasingly be challenged with when to pull the trigger on the use of allogeneic 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.*[9] adds to the growing list of AML scenarios in which 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: (i) it makes sense to use an FLT3 inhibitor to target *FLT3*-ITD when detected in CBF AML; (ii) patients with concurrent trisomy 22 should not be candidates for allogeneic HCT in first complete remission; (iii) close monitoring of MRD, potentially with RT-qPCR performed monthly on blood for at least the first 12 months, is warranted; and (iv) allogeneic HCT should be ready to action early if MRD progression is confirmed.

Disclosures

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Contributions

Both authors wrote and reviewed the paper.

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