Genomics and Transplant Strategies in Pediatric Myeloid Malignancies

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Genetically low risk (LR) pediatric acute myeloid leukemia (AML) comprise core binding factor (CBF) leukemias, and patients with *NPM1* and *CEBPA*-basic leucine zipper mutations. In our recent study, we attempted to clarify whether there is prognostic heterogeneity within LR-AML patients. In our institutional cohort of 78 LR-AML patients, more than half of CBF-AML patients were categorized as intermediate risk for reasons such as concurrent *KIT* mutation. For patients treated with chemotherapy only in first complete remission (CR), there was no clear difference in long-term event-free survival (EFS) when comparing CBF-AML, *CEBPA* (+) and *NPM1* (+) patients. However, the 5-year overall survival was significantly higher for CBF-AML and *CEBPA* (+) patients compared with *NPM1* (+) patients, possibly indicating better response to salvage therapy in these two subgroups.

CBF-AML patients may have diverse cooperating mutations besides the canonical *RUNX1*::*RUNX1T1* or *CBFB*::*MYH11* fusion. *KIT* mutation is the most common concurrent mutation, and our current risk group classification scheme designates CBF-AML patients with *KIT* mutation as genetically intermediate risk. Our previous study showed that the majority of cooperating mutations in *CBFB-MYH11* (+) patients were RAS pathway mutations, whereas *RUNX1-RUNX1T1* (+) patients had a more diverse spectrum of mutations, including those of transcription factors and receptor tyrosine kinase, as well as RAS pathway. Regarding the outcome of these patients, exon 17 *KIT* mutation was the only significant factor for EFS in multivariate study. In addition, patients with *NRAS*/*KRAS* mutations had lower EFS than those lacking these mutations, indicating that the prognosis of individual CBF-AML patients may be further modified according to the presence of these mutations.

The current myeloablative conditioning regimen utilized at our institution for AML patients treated with HSCT consists of total body irradiation 8 Gray, busulfan 130mg/m^2/day for 2 days, and fludarabine 40mg/m^2/day for 4 days. Our recent study found a differing impact of this conditioning regimen according to patient disease status at transplant. High risk AML patients treated with TBI-Bu-Flu-based HSCT in first CR had 5-year EFS of 42.8%, underscoring the current limitations of transplant for therapy of high risk AML. However, patients who relapsed and were then treated with TBI-Bu-Flu-based HSCT in second CR had 5-year EFS of 73.9%, indicating an improved survival rate compared to published literature on outcome of pediatric AML patients who received transplant in second CR.

Overall, detailed genetic evaluation may clearly define risk groups in pediatric AML, with treatment given accordingly. For patients who fail first line treatment and require salvage therapy with HSCT, a TBI-Bu-Flu conditioning regimen may provide favorable outcome in these poor prognosis pediatric AML patients.