Editorial Commentary

Fusion and flow: refining risk prediction in *KMT2A*-rearranged pediatric acute myeloid leukemia

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The treatment of pediatric acute myeloid leukemia (AML) continues to evolve as discovery of new prognostically-relevant genetic alterations shape and refine risk stratification. As treatment options have not significantly changed in recent decades, identification of patients at highest risk of relapse who may benefit from early hematopoietic stem cell transplant (HSCT) has become necessary to minimize disease-related mortality. Until targeted treatments or immunotherapies, including cell adaptive therapies, are successfully developed for AML, HSCT will remain the best chance at long-term cure for many children with AML.

One example of refined risk stratification in AML on the basis of genomics is among those with rearrangements of *KMT2A* (*KMT2A*r), the gene encoding lysine methyltransferase 2A (formerly *MLL*, mixed lineage leukemia). In early AML trials, *KMT2A*r AML was limited to cases with t(9;11)(p21.3;q23.3) which held neither favorable nor unfavorable prognostic significance. With advances in cytogenetic and sequencing technology, it is apparent that *KMT2A* is able to pair with many different genes, with over 100 different fusion partners identified (1,2). A number of recurrent *KMT2A* fusions have emerged as prognostically relevant, with some being definitively associated with poor outcomes (3,4).

Balgobind *et al.* was the first large study to describe the variations in outcome dependent on fusion gene partner in pediatric *KMT2A*r AML (3). They demonstrated that event-free survival (EFS) varied widely, from 11% to 92% and overall survival (OS) between 27–100%, dependent on the precise fusion. In addition, they identified several translocations as predictors of poor prognosis, including t(6;11)(q27;q23), t(10;11)(p12;q23), and t(10;11)(p11.2;q23), in which the *KMT2A* partner genes are *AFDN*, *MLLT10*, and *ABI1*, respectively. Subsequent studies supported these results and further expanded high risk *KMT2A*r AML to include t(4;11)(q21;q23) and t(11;19)(q23;p13.3), with associated fusion partner genes *AFF1* and *MLLT1*, respectively (4-7).

Until recently, most childhood cancer consortia managed all *KMT2A*r AML patients similarly with chemotherapy-based treatment as the standard of care and stem cell transplant in first complete remission (CR1) reserved only for patients with poor initial responses to chemotherapy. The recent data revealing distinct outcomes dependent on the fusion partner have led to the incorporation of distinct *KMT2A* fusions into the risk stratification of recent clinical trials including the ongoing Children's Oncology Group (COG) study AAML1831 (NCT04293562). However, *KMT2A*r AML remains a treatment conundrum, even

as our understanding of this surprisingly diverse group expands. While the recent recognition of distinct outcomes among varying *KMT2A* rearrangements represent a significant improvement, we are still left with essentially two broad *KMT2A*r categories in AML—high risk (HR) and non-high risk (non-HR). Additionally, there are some *KMT2A* fusions so rare that their prognostic impact cannot be reliably estimated from existing data. Therefore, there is still a need to enable further stratification of *KMT2A*r patients as a whole and within the HR and non-HR groups.

In their recent work, van Weelderen *et al*. aimed to achieve this by investigating the impact of measurable residual disease [or minimal residual disease (MRD)] defined by multiparameter flow cytometry on outcomes within *KMT2A*r AML overall and within the two genetically defined subgroups (8). They retrospectively analyzed over 1,200 patients with *KMT2A*r AML, including 456 that had MRD data available after both induction cycles [end of induction 1 (EOI1) and 2 (EOI2)]. Perhaps not surprisingly, this study found that *KMT2A*r patients who were EOI2 MRD negative had better EFS and OS than those who were EOI2 MRD positive. This was true regardless of *KMT2A* risk group. However, while cumulative incidence of relapse (CIR) was lower in EOI2 MRD negative patients within the whole cohort, EOI2 MRD status was less predictive of CIR in non-HR *KMT2A*r patients. Although EOI2 MRD negative status was associated with lower CIR compared to those who were EOI2 MRD positive in the HR group, the CIR for HR patients who were EOI2 MRD negative was 59.6%, indicating a high likelihood of relapse even when an MRD-negative remission is achieved. In addition, the EFS for HR patients who were EOI2 MRD positive was 0% at 5 years, demonstrating dismal outcomes for patients with HR *KMT2A*r who are MRD positive at EOI2. While not all metrics met statistical significance, EOI2 MRD positivity, was associated with worse outcomes in both non-HR and HR groups with HR EOI2 MRD+ patients faring even worse.

Since currently, a primary goal of risk stratification in AML is to identify patients for whom HSCT may improve outcome, one important question van Weelderen *et al*. attempted to address is whether HSCT improves outcomes among *KMT2A*r patients. They found that in their cohort, HSCT in CR1 lowered CIR, particularly amongst genetically defined HR patients, but did not impact OS. However, in patients who were EOI2 MRD positive, HSCT had no impact on CIR or OS. Of course, it is important to note that this analysis is limited by its retrospective design and lack of uniform decision-making on who should receive HSCT in CR1. Thus, these results should not be viewed as definitive evidence that HSCT is not an effective therapeutic modality for this HR population. Hopefully, current clinical trials, including COG AAML1831, which assign patients with HR *KMT2A* fusions to HSCT in CR1, will be able to prospectively define its role in this population.

In all, the authors of this study conclude that EOI2 MRD status is a prognostic factor to be considered in *KMT2A*r AML and that HSCT in CR1 can reduce the risk of relapse in patients with HR *KMT2A* fusions. They further confirm published findings from other groups, demonstrating inferior outcomes for select HR fusions, solidifying the need for aggressive therapy and novel treatment options. Although MRD testing is routinely performed in clinical trials for pediatric AML, prior focus has been on EOI1 MRD results, which are currently used to identify patients with neutral genetics, such as non-HR *KMT2A*r, who would benefit from HSCT. Prior studies have also highlighted the benefit of achieving MRD-negative remission prior to HSCT, as this is associated with lower incidence of relapse and higher OS (9). However, this study is the first to specifically look at impact of EOI2 MRD in the setting of *KMT2A*r AML. As the field is now moving to treat HR *KMT2A*r AML with HSCT, perhaps the most valuable data from this study is the demonstration that for those with non-HR disease, EOI2 MRD can identify patients at high risk for poor outcomes.

There are, however, limitations to this study that should be considered when interpreting the data. Importantly, the data were collected retrospectively from 15 different cooperative groups and 20 different clinical trials lacking uniform treatment regimens and thus had variable outcomes. For example, patients from the largest contributing cooperative group, the COG, which accounted for nearly 40% of the patients in this study, were treated either on the AAML0531 or AAML1031 study. The EFS for these studies varied from 44.8% to 53.1%, depending on the study arm, and thus over-representation of patients from certain studies or study arms may skew the results (10,11). In addition, EOI1 MRD was not included in risk stratification or multivariate analysis despite its common use in existing risk stratification in AML. Interestingly, of the 12 patients who became MRD-positive at EOI2 after initially being MRD-negative at EOI1, 4 of these patients were reported to have an M2 or M3 marrow at EOI1, highlighting potential discrepancies in outcome reporting.

There was also variation in MRD detection methodologies between study groups, as either 4- or 10-color antibody panels were used which may have impacted specificity and sensitivity. Finally, while this study uses an MRD cutoff of <0.1% for MRD-negative status, this cutoff is not uniformly used as some consortia have lowered the threshold to 0.05%, and this study may therefore underestimate the number of patients considered MRD-positive in the current era. Given these limitations, caution should be exercised when using these results to make clinical decisions.

In summary, the findings from van Weelderen *et al*. will help solidify current risk stratification in AML by providing further evidence supporting assignment of genetically defined HR *KMT2A*r AML to high-risk therapies. Further, this study demonstrates that EOI2 MRD is prognostic in *KMT2A*r patients. While the results of this international collaborative study have important implications for the field, ultimately, prospective data using a standardized treatment and risk stratification criteria will be essential to define the best therapeutic approach for this population.

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Footnote

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