Prognostic importance of the fusion partners and measurable residual disease in patients with acute myeloid leukemia who harbor 11q23/*KMT2A* alterations

Krzysztof Mrózek^

Comprehensive Cancer Center, Clara D. Bloomfield Center for Leukemia Outcomes Research, The Ohio State University, Columbus, OH, USA
Correspondence to: Krzysztof Mrózek, MD, PhD. Comprehensive Cancer Center, Clara D. Bloomfield Center for Leukemia Outcomes Research, The Ohio State University, OSU Medical Center, Room 351, 650 Ackerman Rd., Columbus, OH 43202, USA. Email: krzysztof.mrozek@osumc.edu.

Chromosome abnormalities are detected in pretreatment bone marrow and/or blood of most patients diagnosed with acute myeloid leukemia (AML), that is 54% to 60% of adults and 75% to 78% of children with AML (1-3). Several recurring cytogenetic abnormalities and their molecular counterparts are not only used to define distinct entities of AML in the World Health Organization Classification of Haematolymphoid Tumours (4), but have also been repeatedly demonstrated to be among the most important, independent prognostic factors in AML (1-5). In children with AML and abnormal karyotype at diagnosis, the most frequent cytogenetic category comprises rearrangements involving chromosome band 11q23 and the *KMT2A* gene (previously known as *MLL, MLL1, ALL-1, HTRX,* or *HRX*), which occur in 13% to 20% of the patients (1-3), with the highest incidence of approximately 50% among infants aged one year or less (2). The 11q23/*KMT2A* rearrangements are less common in adults, being detected in ~3% to 7% of the patients (6). Although reciprocal translocations predominate, inversions and insertions have also been reported (5-7), and in most instances, these chromosome alterations result in the creation of in-frame gene fusions between *KMT2A* and other partner genes (7). Remarkably,

11q23/*KMT2A* rearrangements are very heterogeneous, with approximately 60 different partner genes found to be fused with the *KMT2A* gene in at least one patient with AML. However, the incidence of particular 11q23/*KMT2A* abnormalities and the partner genes involved varies greatly, and almost one-half of specific partner genes have been hitherto identified in single patients only (7). Among the 11q23/*KMT2A* rearrangements that are recurrent in pediatric AML, the most common by far is t(9;11)(p22;q23) resulting in a *KMT2A::MLLT3* fusion, followed by t(10;11)(p12;q23)/*KMT2A::MLLT10*, t(6;11)(q27;q23)/*KMT2A::AFDN*, t(11;19)(q23;p13.1)/*KMT2A::ELL*, and t(11;19)(q23;p13.3)/*KMT2A::MLLT1* (8).

Several earlier studies have demonstrated associations between the 11q23/*KMT2A* fusion partner and the patients' treatment outcomes. Both among childhood (9-11) and adult (6,12-14) patients with AML, t(9;11)(p22;q23)/*KMT2A::MLLT3* conferred better prognosis than a majority of other 11q23/*KMT2A* rearrangements. Thus, the European LeukemiaNet (ELN) genetic-risk classification, which is widely used to predict response to therapy and help guide treatment decisions, includes patients with t(9;11)(p22;q23)/*KMT2A::MLLT3* in the

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^ ORCID: 0000-0002-1408-5063.

intermediate-risk group, and patients with other balanced rearrangements involving 11q23/*KMT2A* in the adverse-risk group, irrespective of patients' age (15). However, published data indicate the need for a refinement of this prognostic classification. For example, Balgobind *et al.* (8) have shown in a study comprising a relatively large series of children with AML that t(1;11)(q21;q23)/*KMT2A::MLLT11* bestowed a favorable clinical outcome independently from other prognostic factors. Moreover, the relatively favorable prognostic significance of t(9;11)(p22;q23)/*KMT2A::MLLT3* in adults seems to be restricted to those under the age of 60, with patients aged 60 years or older having a much worse outcome that is comparable to the poor outcome of patients with other 11q23/*KMT2A* rearrangements (6,16). Moreover, the prognosis of children with t(9;11)(p22;q23)/*KMT2A::MLLT3* can be adversely affected by the presence of secondary chromosome aberrations additional to the translocation (3), and/or by a marrow morphology that is different from the acute monoblastic leukemia [French-American-British classification M5 (FAB-M5)] (8). Further analyses of the clinical and laboratory characteristics and their correlations with clinical outcomes are needed for patients with AML who harbor 11q23/*KMT2A* rearrangements.

Very recently, van Weelderen *et al.* (17) reported results of a very large collaborative study of children with AML and 11q23/*KMT2A* rearrangements that was initiated by the International Berlin-Frankfurt-Münster Study Group and involved 15 individual pediatric AML study groups/countries. Some results of this study were also presented at the 2020 and 2021 Annual Meetings of the American Society of Hematology (ASH) and published in the abstract form (18,19). The study population comprised initially 1,256 children younger than 19 years who were diagnosed with AML between January 1, 2005, and December 31, 2016, and each carried an 11q23/*KMT2A* rearrangement. The patients were first categorized into subgroups defined by the presence of 1 of 10 relatively common recurrent 11q23/*KMT2A* abnormalities reported by Balgobind *et al.* (8) or into the separate "11q23/*KMT2A*-other" subgroup that contained the remaining patients with rare 11q23/*KMT2A* alterations. The authors then reviewed the latter group and identified two novel subgroups with recurrent 11q23/*KMT2A* rearrangements occurring in more than 10 patients, namely t(X;11)(q24;q23)/*KMT2A::SEPTIN6* and t(1;11)(p32;q23)/*KMT2A::EPS15*. This left 126 cases with infrequent 11q23/*KMT2A* rearrangements, including those with an unidentified fusion partner, in the "11q23/*KMT2A*-

other" subgroup. Because the prognostic significance of the rare rearrangements is currently unknown, the "11q23/*KMT2A*-other" subgroup was excluded from outcome analyses. The remaining 1,130 patients were then divided into two prognostic groups whose outcomes were compared. The high-risk group comprised 402 (35.6%) patients with t(10;11)(p12;q23)/*KMT2A::MLLT10*, t(6;11)(q27;q23)/*KMT2A::AFDN*, t(11;19)(q23;p13.3)/*KMT2A::MLLT1*, t(10;11)(p11.2;q23)/*KMT2A::ABI1* or t(4;11)(q21;q23)/*KMT2A::AFF1*, and the non-high-risk group encompassed 728 (64.4%) patients with t(9;11)(p22;q23)/*KMT2A::MLLT3*, t(11;19)(q23;p13.1)/*KMT2A::ELL*, t(1;11)(q21;q23)/*KMT2A::MLLT11*, t(X;11)(q24;q23)/*KMT2A::SEPTIN6*, t(11;19)(q23;p13), t(1;11)(p32;q23)/*KMT2A::EPS15*, t(11;17)(q23;q21) or t(11;17)(q23;q12)/*KMT2A::MLLT6* (17-19). Importantly, the proportions of patients with the specific aforementioned translocations were not even within either risk-group. In the high-risk group, approximately 54% of the patients harbored t(10;11)(p12;q23)/*KMT2A::MLLT10* and 23% had t(6;11)(q27;q23)/*KMT2A::AFDN*, whereas in the non-high-risk group, roughly 75% of the patients carried t(9;11)(p22;q23)/*KMT2A::MLLT3* and 10% had t(11;19)(q23;p13.1)/*KMT2A::ELL* (17).

Most pretreatment characteristics between the risk groups did not differ significantly, except for a higher median WBC (P=0.0056) in the high-risk group and a trend for the high-risk patients to be aged 10 years or older (P=0.013) as opposed to the patients in the non-high-risk group (17).

A comparison of treatment outcomes revealed that 11q23/*KMT2A* high-risk patients had shorter event-free survival (EFS) (5-year rates, 30.3% versus 54.0%, P<0.0001) and overall survival (OS) (5-year rates, 49.2% versus 70.5%, P<0.0001), and a higher cumulative incidence of relapse (CIR) (59.7% versus 35.2%, P<0.0001) than the non-high-risk patients. The multivariable modeling showed that compared with the 11q23/*KMT2A* non-high-risk patients, those in the high-risk group had approximately two times increased risk of relapse or death. Thus, this largest to-date study (17), with a long follow-up time of 5.2 years (range, 3.5–7.8 years), substantiated the independent unfavorable prognostic impact of the high-risk group defined previously as containing children with translocations between 11q23/*KMT2A* and such translocation partners as 10p12, 6q27, 19p13.3, 10p11.2 and 4q21 (8,18,20).

The novel aspect of the study by van Weelderen *et al.* (17) is its demonstration of a prognostic value of analyzing the

flow cytometry-based measurable residual disease (flow-MRD) together with the 11q23/*KMT2A* fusion partner. Because not all participating study groups could provide flow-MRD data, only approximately 40% of 1,130 patients included in the outcome analyses had flow-MRD data available at both the end of remission induction course 1 (EOI1) and at the end of course 2 (EOI2). Among these 456 patients, 413 (90.6%) were deemed to be EOI2 flow-MRD-negative, i.e., had MRD levels <0.1% at both EOI1 and EOI2 (362 patients) or at EOI2 following positivity at EOI1 (51 patients). The remaining 43 (9.4%) patients had MRD levels ≥0.1% at both EOI1 and EOI2 (31 patients) or at EOI2 after a negative result at EOI1 (12 patients) and were thus considered positive for EOI2 flow-MRD responses. These patients had shorter EFS (5-year rates, 16.3% versus 47.6%, P<0.0001) and OS (5-year rates, 27.9% versus 66.0%, P<0.0001) and tended to have a higher CIR (65.4% versus 46.1%, P=0.016) than patients with EOI2 flow-MRD negativity. Likewise, EFS and OS, but not CIR, were also significantly worse for patients with EOI2 flow-MRD positivity within both the 11q23/*KMT2A* high-risk and the non-high-risk patient groups. Moreover, in the larger group of patients who were negative for flow-MRD at EOI2, those classified in the 11q23/*KMT2A* high-risk group had worse EFS (5-year rates, 34.6% versus 55.9%, P<0.0001) and OS (5-year rates, 52.3% versus 74.8%, P<0.0001) and higher CIR (59.6% versus 37.5% P<0.0001) than patients in 11q23/*KMT2A* non-high-risk group. On the other hand, there were no significant differences in OS and CIR between the 11q23/*KMT2A* high- and non-high-risk groups among patients with flow-MRD positivity at EOI2, albeit children in the 11q23/*KMT2A* high-risk group tended to have a shorter EFS than those classified in the non-high-risk group (5-year rates, 0% versus 30.4%, P=0.011). The authors demonstrated the independent prognostic importance of flow-MRD response and 11q23/*KMT2A* fusion partner group by performing multivariable analyses, in which both the EOI2 flow-MRD positivity and 11q23/*KMT2A* high-risk group were associated with significantly worse EFS, OS and CIR, whereas age 10 years or more was associated with shorter OS (17).

The collaborative multinational nature of the study by van Weelderen *et al.* (17) enabled collection of data on a large number of children with a relatively rare disease, which would otherwise be impossible at a single institution. Still, even in this very large cohort of patients with 11q23/*KMT2A*-rearranged AML, some specific 11q23/*KMT2A* alterations were quite infrequent, such as t(11;17)(q23;q12)

found in 10 patients, t(4;11)(q21;q23) detected in 12 patients, or t(11;17)(q23;q21) and t(1;11)(p32;q23), which were present in 13 patients each. With the exception of t(4;11)(q21;q23), the aforementioned translocations were included in the 11q23/*KMT2A* non-high-risk group based on the outcome data presented by the authors at the 2020 ASH Annual Meeting (18). However, it seems reasonable to wait for the collection of outcome data on greater numbers of children with these translocations in future studies before conclusively defining their prognostic impact, as illustrated by the example of the relatively infrequent t(1;11)(q21;q23). This rearrangement has been previously reported to independently confer favorable prognosis (8), but this could not be confirmed in the patient population analyzed by van Weelderen *et al.* (18). Additionally, I suggest exclusion from the future studies of the subset defined by the presence of "t(11;19)(q23;p13)", which comprised 3% (23 patients) of the 11q23/*KMT2A* non-high-risk group (17). This subset appears to include a mixture of patients with t(11;19)(q23;p13.1)/*KMT2A*::*ELL* and those with t(11;19)(q23;p13.3)/*KMT2A*::*MLLT1* for whom the precise breakpoint at 19p was not established. Since the former translocation denotes non-high-risk and the latter high-risk grouping (17), and the previously published data show that each of these translocations is associated with unique molecular genetic and clinical features (6,21), they should not be considered to represent a single rearrangement. If the determination of the exact breakpoint at 19p13 is not possible, patients with "t(11;19)(q23;p13)" should rather be included in the "11q23/*KMT2A*-other" subgroup whose prognostic impact is presently not known.

Additionally, future studies should continue to investigate the prognostic impact of secondary (additional) chromosome aberrations accompanying 11q23/*KMT2A* rearrangements. In their 2021 ASH abstract, van Weelderen *et al.* (19) compared the outcome of patients with secondary chromosome abnormalities at diagnosis with the outcome of patients who had the 11q23/*KMT2A* rearrangements as the only cytogenetic change. Multivariable analysis of the entire patient cohort revealed that the presence of any secondary aberration was independently associated with inferior OS, but not with disease-free survival (19). However, it has been previously shown that the patterns of secondary chromosome aberrations vary among different recurring 11q23/*KMT2A* alterations (12,21,22). For instance, t(6;11)(q27;q23) and t(11;19)(q23;p13.1) occur most often, in 85% to 90% of patients, as the sole chromosome abnormality, whereas as many as 60% of patients with t(11;19)

(q23;p13.3) and one-half of those with t(10;11)(p12;q23) or t(2;11)(p21;q23) carry secondary abnormalities (22). Furthermore, although trisomy of chromosome 8 is the most frequent additional aberration in patients with t(4;11)(q21;q23), t(9;11)(p22;q23), t(10;11)(p12;q23), t(11;17)(q23;q12-21), t(11;17)(q23;q25), and t(11;19)(q23;p13.3), in patients with t(2;11)(p21;q23) it is del(5q) and in patients with t(1;11)(q21;q23) trisomy of chromosome 19 that are the predominant secondary changes (21,22). Hence, it is important for future large studies to investigate the prognostic significance of specific secondary chromosome aberrations in patients with particular recurrent 11q23/*KMT2A* rearrangements. Likewise, even though patients with 11q23/*KMT2A* rearrangements have in general a relatively low number of additional gene mutations, with mutations in genes in the RAS (rat sarcoma virus) pathway, such as *KRAS*, *NRAS*, and *PTPN11*, being the most common (6), further studies should also assess the potential influence of the presence of these mutations on the patients' clinical outcomes.

It has been well-established that prognostic factors depend on the type of therapy used, and cytogenetic and molecular genetic abnormalities that bestow an unfavorable prognosis with one therapeutic approach may lose their adverse prognostic impact when another treatment is used. Previous studies in adults with 11q23/*KMT2A* alterations suggested that allogeneic hematopoietic stem-cell transplantation (allo-HSCT) can, in some cases, improve their outcome (14,23). In the study by van Weelderen *et al.* (17), almost 21% of children who achieved a complete remission (CR) received allo-HSCT in the first CR, and although this resulted in a lower risk of relapse in the high-risk patient group, OS was not significantly improved, likely because of the toxicity of this therapy. The authors pointed out that the results of their study underline the need for novel therapeutic strategies (17), such as the addition of gemtuzumab ozogamicin to induction therapy that was recently shown to improve outcomes of children with 11q23/*KMT2A* rearrangements (20), and/or the use of small-molecule inhibitors of the menin-KMT2A interaction shown not only to substantially decrease leukemic cell burden in the xenograft mouse models derived from patients with 11q23/*KMT2A*-rearranged acute leukemia (24), but also to be capable of inducing CR or CR with partial hematologic recovery and clearance of minimal residual disease in heavily pretreated pediatric and adult patients with refractory or relapsed disease (25). It is at present not fully understood whether the kind of 11q23/*KMT2A*

fusion partner can influence the efficacy of treatment with inhibitors of the menin-*KMT2A* interaction in a manner similar to that in children receiving standard therapy, as reported by van Weelderen *et al.* (17).

In conclusion, the study by van Weelderen *et al.* (17) convincingly demonstrates the prognostic value of combining a risk-group assignment based on the 11q23/*KMT2A* fusion partner with the flow-MRD response at the end of the second course of remission induction. This has been achieved despite the use of, as the authors put it, "the relatively old and largely non-standardized flow-MRD data" in their study (17). It is likely that the sensitivity of MRD detection can be improved by the use of state-of-the-art ten or more color flow cytometry or innovative molecular techniques. It is also noteworthy that as many as 10% of the patients could not be assigned to the 11q23/*KMT2A* risk group because they harbored very rare translocations or inversions whose impact on treatment outcome is at present unknown. Therefore, a continuation of large multinational cooperative studies is of utmost importance for identifying additional patients with these rare rearrangements and correlating these rearrangements with response rates, response duration, and survival in the context of both current and novel induction and postremission therapeutic approaches.

Footnote

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