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Acute Myeloid Leukemia with 11q23 Rearrangements: A Study of Therapy-Related Disease and Therapeutic Outcomes

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Abstract

We described the clinical features and outcomes for 63 adult patients with acute myeloid leukemia (AML) with a reciprocal translocation involving the 11q23 locus (*MLL*) who were treated at Memorial Sloan Kettering Cancer Center (MSK). The population included 40 female (63%) and 23 male (37%) patients, with a median age of 51 years old (range 18–82 years). Of the 31 patients who had had an antecedent malignancy, 14 (45%) had had breast cancer or DCIS and 22 (71%) had received anthracycline-based systemic chemotherapy. The translocation partner for the 11q23 rearrangement was identified in 60 of the 63 patients (95%) studied. The distribution of translocation partners differed for those who had previously received cytotoxic chemotherapy. Most patients with therapy-related disease had a 9p22 or 19p13 partner, as compared to those with de novo disease (95% vs. 68%, $p = 0.023$). Of the 30 patients who received all therapy under observation, 15 (50%) patients had de novo disease and 15 (50%) had received antecedent chemotherapy. No significant difference in survival was observed between groups ($p = 0.44$). Twenty-two patients received induction as up-front therapy, of whom 11 (50%) achieved CR / CRi. The achievement of CR/CRi with one course of induction was associated with improved OS, with a 6-month OS of 73% as compared to 23% for those who did not ($p = 0.018$). The achievement of CR / CRi with a single course of induction may be a marker of favorable survival in this subtype of high-risk AML.

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Authorship Contributions:

KM –reviewed potential patients for inclusion, extracted data from the EMR, performed the descriptive analysis, wrote the manuscript

YZ –performed cytogenetic evaluation on all included patients, assisted with literature review, edited the manuscript

CF –extracted potential patients from EMR

SD –performed survival analysis and provided statistical oversight

MT –oversaw the project, provided guidance and direction, helped with manuscript preparation

All authors reviewed and agreed prior to submission of the manuscript.

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Keywords

MLL; KMT2A; 11q23; AML; cytogenetics; therapy-related myeloid neoplasm

1. Introduction:

Structural abnormalities involving the long arm of chromosome 11, region 2, band 3 (11q23), are cytogenetic changes consistently seen in hematopoietic malignancies, including acute myeloid leukemia (AML)¹. Leukemias bearing translocations at 11q23 stem from changes to a histone 3 lysine 4 methyltransferase at that site which is involved in the epigenetic regulation of hematopoietic cells. Previously termed the *Mixed Lineage Leukemia (MLL)* gene, it is now known as the *Lysine [K]-specific Methyltransferase 2A (KMT2A)* gene, a name which is more reflective of its function². Translocations at this locus lead to proteins containing the amino terminal portion of *KMT2A* fused to the carboxy terminal portion of a fusion partner, of which at least 135 have been described³. These fusion proteins may lead to changes in epigenetic regulation of hematopoietic cells that cause a differentiation block and facilitate leukemogenesis.

Translocations of 11q23 are seen in approximately 5–10% of adult AML^{4,5}. The most common translocation partners include t(9;11)(p22;q23) or *AF9*; t(11;19)(q23;p13.3) or *ENL*; t(10;11)(p12;q23) or *AF10*; t(6;11)(q27;q23) or *AF6*; and t(11;19)(q23;p13.1) or *ELL*^{3,6,7}. While the median age at diagnosis for AML is 68 years old, the median age for those with 11q23 translocations is in the early 50s⁵. This cytogenetic abnormality is also commonly seen in patients with therapy-related AML, specifically one to three years after treatment with chemotherapy regimens containing anthracyclines or other topoisomerase II inhibitors⁸. Given that women commonly receive anthracyclines as part of breast cancer treatment, therapy-related 11q23 abnormalities can often be seen more commonly in women⁹. Translocations of 11q23 can also be sufficient to make the diagnosis of AML with myelodysplasia-related changes; balanced 11q23 translocations with either 16p13.3 or 2p21 fall into this category, as per the WHO^{10,11}.

In terms of risk stratification, 11q23 abnormalities as a whole have a worse overall survival than other gene fusions commonly seen in AML, including inv(16), t(15;17), and t(8;21), and a comparable survival to t(6;9)⁴. Whether or not all 11q23 abnormalities should be considered as having equally poor prognosis has been of some debate in the literature. Risk stratification in 1998 based on the AML MRC 10 trial suggested that 11q23 abnormalities should all be categorized as intermediate risk, whereas the 2000 SWOG / ECOG classification system considered all 11q abnormalities as unfavorable^{12,13}. A refinement of the MRC criteria in 2010 considered both t(9;11)(p21~p22;q23) and t(11;19)(q23;p13) to be intermediate risk, with the remaining translocation partners of 11q23 considered to be adverse. No distinction was made between 19p13.3 (*MLL-ENL*) and 19p13.1 (*MLL-ELL*), and an analysis by the Cancer and Leukemia Group B (CALGB) / Alliance of Clinical Trials in Oncology (Alliance) found no significant differences were found in terms of disease-free or overall survival between these two groups^{14,15}. The more

recent classification system by the European LeukemiaNet considers *AF9* to be intermediate risk and all other 11q23 translocations to be adverse¹¹.

While the translocation partner appears to be important for predicting outcomes from the time of diagnosis, it also appears to be of prognostic significance in patients who undergo hematopoietic stem cell transplantation. One previous study found that post-HSCT outcomes were best for patients with t(9;11) and t(11;19), but worse for those with t(6;11) and t(10;11)¹⁶. How best to risk stratify these patients, and whether t(9;11) and t(11;19) should both be considered intermediate risk, remains an ongoing conversation in the field^{17,18}.

Here we examine cases of 11q23-rearranged AML treated at our institution over a 21-year period and discuss the implications for our understanding of this disease, its prognosis, and its treatment.

2. Patients and Methods:

2.1. Patient identification

Patients who were treated at Memorial Sloan Kettering Cancer Center between December 1996 and November 2017 were considered for inclusion. Patients who had a diagnosis of acute myeloid leukemia with the presence of an 11q23 translocation were identified by a search of the electronic medical record. Translocations involving the 11q23 locus were detected in bone marrow and / or peripheral blood samples using karyotyping, fluorescence in-situ hybridization test with an MLL break-apart probe assay, and gene-fusion testing. The upper limit of normal variation for the FISH probe was 1.4%; only rearrangements seen above this level were considered. The cytogenetic data of all patients were manually confirmed and verified.

Additional patients were identified based on a manual review of the cytogenetics database by the director of the MSK cytogenetics laboratory. Patients with deletions, additions, or partial tandem duplications of 11q23 were excluded, as were patients under 18 years of age at the time of AML diagnosis. Only patients with AML were studied; patients with ALL, multiple myeloma, solid tumors, or other malignancies with 11q23 translocations were excluded.

2.2. Data collection

Patient data was retrospectively collected in accordance with IRB approval. Patient demographics, information on any antecedent malignancies and therapies, date of AML diagnosis, 11q23 translocation partner, presence or absence of extramedullary and CNS disease, therapies for AML and responses, pathology results from bone marrow aspirations and biopsies, and data on bone marrow transplantation, outcomes, and subsequent therapies were manually abstracted from the electronic medical record.

2.3. Statistical analysis

Composite complete remission, incorporating both complete remission (CR) and complete remission with incomplete hematologic recovery (CR_i) was determined per the 2017 ELN recommendations. Kaplan-Meier methods and the log-rank test were used to estimate and

compare overall survival from the date of the induction response assessment based on response achieved. The analysis was performed only for patients who received induction therapy at MSK. Descriptions were provided of the analysis of other clinical, laboratory, and pharmacologic variables.

3. Results:

3.1. Patient characteristics

Sixty-three adult patients, 40 female and 23 male, were identified as having been treated for 11q23-rearranged acute myeloid leukemia at our institution between December 1996 and November 2017 (Table 1). The median age was just over 51 years, with a range of 18–82 years (Figure 1). There were almost twice as many female as male patients. Twelve (30%) of the 40 female patients had been treated with chemotherapy for breast cancer.

Full diagnostic karyotypes were available in 51 patients, of whom 14 had additional cytogenetic abnormalities including 5 patients with complex karyotype and 5 with trisomy 8.

3.2. Secondary AML After Antecedent Malignancies

Thirty-one patients had had one or more antecedent malignancies (Table 2). Sixteen patients had an antecedent hematopoietic malignancy, including chronic myelomonocytic leukemia (4 patients), diffuse large B-cell lymphoma (4 patients), myelodysplastic syndrome (4 patients), chronic myeloid leukemia (2 patients), APL (1 patient), Langerhans cell histiocytosis (1 patient), and prior peripheral T-cell lymphoma (1 patient). One patient had had both DLBCL and MDS. Solid tumor malignancies were seen in 20 patients and included DCIS / breast cancer (14 patients), Ewing sarcoma / osteosarcoma / primary osteogenic sarcoma (5 patients), and endometrial adenocarcinoma (1 patient).

3.3. Prior Therapy for Antecedent Malignancies

Twenty-seven patients had had prior cancer-directed therapy, including 22 patients who had had prior anthracycline exposure. Sixteen patients had undergone radiation therapy prior to being diagnosed with MLL AML.

The exact or approximate start date of the prior chemotherapy regimen was available for 21 of the 22 patients who had previously received anthracyclines. The median time between therapy initiation for the antecedent malignancy and AML diagnosis for these patients who received anthracycline-based chemotherapy was 21.4 months, with a range of 10.5 to 54.4 months (Figure 2).

Extramedullary disease was seen in 7 patients (11.1%) and CNS disease in 4 patients (6.3%).

3.4. Translocation Partners for 11q23 in *de novo* and Secondary AML

The translocation partner for the 11q23 rearrangement was identified in 60 of the 63 patients studied (95%) (Figure 3A). Translocation involving 9p22 was the most frequent, found in 31 patients (51%), followed by 19p13.1 in 11 patients (18%), 6q27 in 6 patients (10%), 19p13.3

in 3 patients (5%), and the remaining 1p36, 1p32, 3p21, 4q21, 10p12, 15q15, 17q21, 17q25 and an undefined 19p13 occurring in one patient each (1–2%).

The distribution of translocation partners differed between those with *de novo* disease and those who had previously received cytotoxic chemotherapy (Figures 3B and 3C). Among 40 patients with *de novo* disease, 17 (41%) had a reciprocal translocation with 9p22, 6 (15%) with 6q27, 10 (25%) with 19p13 (including both 19p13.1 and 19p13.3), and 1 patient each (2–3%) with 1p32, 3p21, 4q21, 10p12, 15q15, 17q21, and 17q25. For the 20 patients with therapy-related AML, 14 (71%) had a reciprocal translocation with 9p22, 5 (24%) with 19p13, and 1 (5%) with 1p36. Overall, 95% of patients with t-AML had 9p22 or 19p13 as a translocation partner as compared to 68% of *de novo* AML patients ($p = 0.018$).

3.5. Treatment

Thirty patients received their initial therapy at MSK (Table 3). Of these, 22 underwent induction chemotherapy (74%) and the remaining 8 were treated with the DOT1L inhibitor pinometostat, low-dose cytarabine (LoDAC), hypomethylating agent (HMA) therapy, or supportive care alone. Eleven of the 22 patients who received induction therapy achieved a complete remission or a complete remission with incomplete hematologic recovery. Of the 11 patients (50%) who did not achieve a CR / CRi, seven received a second induction regimen and two of these patients (25%) achieved an MRD-positive CR. In total, of the 22 patients who received induction therapy, 13 (59%) achieved a CR / CRi, with the remaining 9 (41%) having refractory disease or death prior to evaluation of response. None of the patients who received non-induction initial treatment achieved a CR.

Patients who achieved CR / CRi after first induction had a significant improvement in OS as compared to patients who did not (Figure 4). Those who achieved CR after a single course of induction had an improved 6-month overall survival of 73% (95% CI 51–99%) as compared to 23% for those who did not (95% CI 7–77%) with $p = 0.018$. The achievement of CR / CRi after the first induction was seen in 45% of patients with a 9p22 translocation partner and in 41% of patients with any other translocation partner (Figure 5). For patients with a 19p13.3, the CR / CRi rate was the highest at 67%; for those with a 6q27, the CR / CRi rate was the lowest at 17%. The same was true when those who achieved CR / CRi with either first or second induction were included together. Of the 14 patients with therapy-related disease who were treated at MSK, 6 achieved a CR / CRi (43%).

Fifteen patients treated at MSK had *de novo* disease and 15 had received antecedent chemotherapy. No significant difference in survival was observed ($p = 0.44$).

In total, 12 patients went on to allogeneic hematopoietic stem cell transplantation –6 (50%) with 9p22, 3 (25%) with 19p13.3, one (8%) with 19p13.1, one (8%) with 19p13 undefined, and one (8%) with 1p32 translocation partner. Seven patients had 9/10 or 10/10 matched unrelated donors, two had matched related donors, two had haplotype matched donors, and one had a double umbilical cord blood transplant. Seven patients had myeloablative conditioning (four with total-body irradiation, thiotepa, and cyclophosphamide and three with busulfan, melphalan, and fludarabine) and five had reduced-intensity conditioning (two

with Mel / Flu, one with Flu / Cy / nonablative TBI, and one with Mel / Flu / thiotepa per protocol).

Three of 12 patients (25%) relapsed, two after myeloablative conditioning for a MUD transplant and one after non-ablative conditioning for a haplotype transplant. One patient had a 9p22 translocation partner, the other two had 19p13.3.

The 19p13.3 patient who relapsed after a haplotype transplant had known residual disease prior to transplant; they received one cycle of azacitidine after relapse but did not respond. The MUD HSCT patient with a 9p22 partner was re-treated with 7+3, achieved an MRD-positive CR, and underwent a second transplant.

4. Discussion:

This study of 63 patients with *MLL*-rearranged AML treated at our center between 1996 and 2017 demonstrates that most patients with therapy-related *MLL*-rearranged AML had a t(9;11) or t(11;19) and that a greater diversity of translocation partners was seen for those with *de novo* disease. We also detected no difference in survival between *MLL*-rearranged patients with *de novo* vs. therapy-related disease. Finally, we found that response to a single course of induction therapy may separate patients into chemosensitive and chemoinensitive phenotypes, with implications for overall survival.

Patients with therapy-related AML are thought to have worse outcomes than those with *de novo* disease overall, but our study reinforces that therapy-related disease should be approached with nuance⁹. One prior study of 40 *de novo MLL* patients with 11 therapy-related *MLL* patients by Schoch et al. found that those with therapy-related *MLL* AML had a median OS of approximately 3 months as compared to approximately one year for those with *de novo* disease, $p = 0.0143$ ¹⁹. That study, however, did not look at the role of translocation partners in determining survival.

In our cohort, we found that most patients with therapy-related AML had t(9;11) or t(11;19). Patients with t(9;11) are thought to have an intermediate-risk disease phenotype in the *de novo* setting. Variably, t(11;19) has also been described as intermediate risk, however some controversy exists in the literature^{11,14,16}. The preponderance of intermediate-risk translocation partners in our therapy-related cohort may partially explain why overall survival was no worse in this group as compared to those with *de novo MLL* AML.

Translocation t(9;11) has previously been described as the most common *MLL* rearrangement in tAML, as by Kayser et al. in 2011. They found that t(9;11) was present in 11% of their tAML cases but only 1% of their *de novo* cases, $p < 0.0001$. They aggregated the data for the remaining *MLL* translocation partners and did not find a difference between the two groups, $p = .07$ ⁹. Our study adds to this finding, as 95% of our therapy-related *MLL* AML patients had t(9;11) or t(11;19), suggesting that there is significantly less translocation partner diversity among patients with therapy-related disease.

We also found that achievement of CR (including CRi) after one course of induction also significantly improved survival. Whereas most consider a failure to achieve a reduction in

blast percentage or CR after two induction therapies to be primary refractory disease, there is reason to believe that achievement of CR / CRi after one course of induction may be indicative of chemosensitivity^{11,20–22}. Patients with *MLL*-rearranged disease who do not achieve CR/CRi with a single course of induction may be chemo-insensitive to further courses, which may explain their decreased OS.

The median age at diagnosis of our cohort was around 51 years, which may be reflective of data from previous studies that suggested that 11q23-rearranged AML disproportionately affected patients who are between 30 and 50 years of age^{3,19}. We did note the wide distribution of age, including patients just over 18 and those up 82 years old. However, when binned by age in 10-year strata, it appeared that there was a peak in the 49–59 year old group and a relative decrease in occurrence in patients over 69 years old, with the remaining groups being relatively evenly distributed. This distribution may partially be explained by the fact that this heterogeneous population included secondary AML patients who had been treated for pediatric tumors as well as breast cancer, in addition to patients with de novo AML.

Karyotypic abnormalities involving 11q23 translocations may co-occur with complex cytogenetics, as was seen in almost 10% of our cohort. It is unclear how, if at all, the presence of other abnormalities affects the biology and clinical trajectory of these patients. Previous studies have suggested that t(9;11) may do just as well or better when additional cytogenetic abnormalities are present, while others suggest that additional cytogenetic abnormalities may portend worse outcomes in pediatric cases^{14,23}. A limitation of our study is the small number of patients in our cohort who were found to have both an *MLL* rearrangement and an additional cytogenetic abnormality or complex karyotype. As it stands, the impact of complex karyotype in adult 11q23-rearranged AML remains an unanswered question in the field.

Similarly, trisomy 8 was seen with some frequency in this cohort. While this is known to be the most frequent cytogenetic abnormality in AML, it has also been shown to be of importance in 11q23-rearranged AML²⁴. The presence of an 11q23 rearrangement is known to be associated with increased ecotropic viral integration 1 (*EVII*) gene expression, which is associated with decreased event-free, relapse-free, and overall survival. Patients with 11q23 rearrangements who are negative for *EVII* overexpression are frequently found to have a concurrent trisomy 8 and have a better prognosis²⁵. Further studies are needed to better characterize this finding, understand its relevance as a clinical biomarker, and evaluate whether or not this may lend itself to the development of therapies targeted against the *EVII* overexpression in 11q23-rearranged AML.

MLL rearrangements are relatively infrequent in AML, occurring in only 5–10% of patients with the disease. In an effort to capture as many cases as possible, we expanded our search to include patients over a 21-year period. This allowed us to study a larger cohort, however we could not control for variations in practice patterns over that time period or their effects on patient outcomes. Additionally, despite our search of the medical record and manual curation of cytogenetics data, our single-center cohort is still smaller than other published series^{5,9}. While this may reflect the relatively low frequency of this disease, it may also

suggest that patients with *MLL* rearrangements in our catchment area may be less likely to be referred to a subspecialty center such as ours. It may also be indicative of the difficulty of detecting these patients with FISH or cytogenetics in the setting of cryptic fusions, leading to false-negative results for 11q23 rearrangements. While molecular data was not available for most of our patients given the time period over which the study was done, the increasing use of NGS technology and follow-up studies using single-nucleotide polymorphism (SNP) arrays may increase future detection of *MLL* rearrangements.

In conclusion, our work has two central findings. First, most of our patients with therapy-related *MLL* rearrangements had either a t(9;11) or a t(11;19), with increased diversity in translocation partner seen among those with *de novo* disease. No difference in OS was seen between tAML and *de novo* AML in our study.

Our second main finding is that achievement of CR after a single round of induction therapy stratified patients in terms of chemosensitivity. We detected a significant difference among groups that suggests that chemosensitivity may be a predictive indicator of overall survival in patients with *MLL*-rearranged AML.

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Highlights

- *MLL* rearrangements can occur in either the *de novo* or therapy-related setting
- Most patients with therapy-related *MLL*-r AML had a t(9;11) or t(11;19)
- *De novo MLL*-r AML patients had a greater diversity of translocation partners
- No difference in OS was seen between tAML and *de novo MLL* AML
- Response to initial induction therapy was associated with improved survival

Key Points:

- Most patients with therapy-related *MLL*-r AML had a t(9;11) or t(11;19); *de novo MLL*-r AML patients had a greater diversity of translocation partners
- Response to a single induction was associated with chemosensitivity and favorable survival in this population

Figure 1. Distribution of Age at AML Diagnosis:

Distribution of patients by age at the time of diagnosis with 11q23-rearranged AML.

Figure 2. Months Between Prior Anthracycline Use and AML Diagnosis for *MLL* tAML Patients

The approximate start date of therapy was available for 21 of 22 patients who had received an anthracycline for a prior malignancy; each patient is represented on the x-axis. The duration, in months, between the start of prior anthracycline treatment and the date of AML diagnosis is represented on the y-axis. The median time to AML diagnosis was 21.4 months, with a range of 10.5 to 54.4 months.

Figure 3. Translocation Partners in All Patients, *de novo* AML, and Therapy-Related AML

A: 11q23 Translocation partners for 60 patients under study for whom a translocation partner was identified. B: Breakdown of 11q23 translocation partners for those with *de novo* disease. C: Breakdown of translocation partners for patients with therapy-related AML. Patients with tAML were significantly more likely to have a translocation with 9p22 than with any other partner.

Figure 4. Overall Survival Stratified by Achievement of CR / CRi after First Induction
 Estimated Kaplan-Meier survival for patients treated at MSKCC stratified by whether or not they achieved a CR after their first round of induction therapy

Figure 5. Achievement of CR / CRi after First Induction by Translocation Partner

Total number of patients with each translocation and total number who achieved CR after first induction. There was no significant difference in the CR rate for patients with 9p22 as compared to other translocation partners.

Table 1.

Patient Characteristics

Total Number of Patients		63	
Median age in years (range)		51.1 (18.9–82.6)	
Sex		No. Patients	Percentage
Female		40	63%
Male		23	37%
Prior Malignancy			
Total		31	49%
Antecedent hematopoietic malignancy		15	24%
Antecedent solid tumor malignancy		20	32%
Prior Cancer-directed Therapy			
Total		27	43%
Prior Anthracycline Exposure		22	35%
Prior Radiation Exposure		16	25%
Cytogenetics			
Full Diagnostic Karyotype		51	81%
Additional Cytogenetic Abnormalities		14	27%
Complex Karyotype (≥ 3)		5	10%
Trisomy 8		5	10%

Table 2.

Hematologic and Solid Tumor Malignancies Present Prior to AML Diagnosis

Total Number of Patients	31
Prior Hematologic Malignancy	
Total	16
CMML	4
DLBCL	4
MDS	4
CML	2
APL	1
Langerhans Cell Histiocytosis	1
Peripheral T-cell Lymphoma	1
Prior Solid Tumor Malignancy	
Total	20
DCIS / Breast Cancer	14
Primary Osteogenic Sarcoma /	
Osteosarcoma / Ewing's Sarcoma	5
Endometrial Adenocarcinoma	1

Table 3.**Treatments and Outcomes**

Received Initial Leukemia Treatment at MSKCC	30	
Initial Induction	22	73%
7+3	11	50%
7+3+dasatinib	1	5%
7+3, single dose of vinblastine	1	5%
5+3	2	9%
Capizzi II	3	14%
Mitoxantrone and Cytarabine	2	9%
TVTC	1	5%
CPX-351	1	5%
Non-Induction Initial Treatment	8	27%
DOT1L Inhibitor	1	13%
LoDAC	1	13%
HMA	3	38%
Supportive Care	3	38%
CR to Initial Induction	11	50%
< CR to Initial Induction	10	45%
Death	1	5%
Second Induction	7	78%
I-DAC	1	14%
Mitoxantrone and Cytarabine	1	14%
DOT1L Inhibitor	1	14%
HiDAC	2	29%
FLAG-Ida	1	14%
Transplant	1	14%
CR to Second Induction	2	29%
CR to First or Second Induction	13	59%