Outcomes of Acute Lymphoblastic Leukemia with KMT2A (MLL) rearrangement – The MD Anderson Experience

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Abstract:
Acute lymphoblastic leukemia (ALL) with t(4;11)(q21;q23) – KMT2A-AFF1 is associated with a poor prognosis. The impact of KMT2A rearrangements other than t(4;11) is uncertain and the benefit of allogeneic stem cell transplant (HSCT) is unclear. We reviewed adult patients with ALL treated at our institution from 1984 to 2019 and identified 50/1102 (5%) with KMT2A rearrangement: 42 (84%) with t(4;11)/KMT2A-AFF1 and 8 (16%) with other gene partners. The median age was 45 years old (range, 18 - 78 years); median white blood cell count was 109.0 x 10^9/L (range, 0.5 - 1573.0). The complete remission (CR) rate was 88% and the rate of measurable residual disease negativity by flow cytometry at CR was 41% (76% overall during follow-up). At the last follow-up, 14 patients were alive. The 5-year overall survival (OS) rate was 18% (95% CI, 9 - 35%) with no difference between t(4;11) and other KMT2A rearrangements (p=0.87). In a 4-month landmark analysis, the 5-year OS rate was 32% (95% CI, 14 - 70%) in patients who underwent HSCT versus 11% (95% CI, 3 - 39) in others (p=0.10). Our study confirms the poor prognosis of ALL with any KMT2A rearrangement and the role of HSCT in these patients.

Conflict of interest: COI declared - see note

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Key Points

- ALL with KMT2A rearrangement is associated with a poor prognosis, irrespective of the gene partner involved.
- All patients with KMT2A-rearranged ALL benefit from allogeneic hematopoietic stem cell transplant in first remission.

Abstract

Acute lymphoblastic leukemia (ALL) with t(4;11)(q21;q23) – KMT2A-AFF1 is associated with a poor prognosis. The impact of KMT2A rearrangements other than t(4;11) is uncertain and the benefit of allogeneic stem cell transplant (HSCT) is unclear. We reviewed adult patients with ALL treated at our institution from 1984 to 2019 and identified 50/1102 (5%) with KMT2A rearrangement: 42 (84%) with t(4;11)/KMT2A-AFF1 and 8 (16%) with other gene partners. The median age was 45 years old (range, 18 – 78 years); median white blood cell count was 109.0 x 10^9/L (range, 0.5 – 1573.0). The complete remission (CR) rate was 88% and the rate of measurable residual disease negativity by flow cytometry at CR was 41% (76% overall during follow-up). At the last follow-up, 14 patients were alive. The 5-year overall survival (OS) rate was 18% (95% CI, 9 – 35%) with no difference between t(4;11) and other KMT2A rearrangements (p=0.87). In a 4-month landmark analysis, the 5-year OS rate was 32% (95% CI, 14 – 70%) in patients who underwent HSCT versus 11% (95% CI, 3 – 39) in others (p=0.10). Our study confirms the poor prognosis of ALL with any KMT2A rearrangement and the role of HSCT in these patients.
Introduction

Cytogenetic abnormalities are associated with prognosis in acute lymphoblastic leukemia (ALL)\(^1\)\(^-\)\(^3\). High-risk cytogenetics include complex karyotype (≥5 abnormalities), low-hypodiploidy / near-triploidy, t(9;22)/BCR-ABL1 and 11q23/KMT2A rearrangements. The most frequent gene partner involved in KMT2A-rearranged ALL is AFF1 on chromosome 4q21. ALL with t(4;11)(q21;q23) – KMT2A-AFF1 has a poor prognosis, and patients with this translocation are offered allogeneic stem cell transplantation (HSCT) in first complete remission (CR1). More than 130 gene partners have been described with KMT2A rearrangements in leukemia\(^4\). The frequency and prognostic significance of the various gene partners in KMT2A-rearranged ALL are not well defined, and it is uncertain whether all these patients should be offered HSCT in CR1. We report herein on the characteristics and outcomes of patients with KMT2A-rearranged ALL, and on the impact of HSCT in CR1.

Methods

We reviewed 1102 patients with newly diagnosed ALL treated at our institution from 1984 to 2019 to identify patients with KMT2A rearrangement. The presence of t(11;v)(q23;v) was assessed by conventional cytogenetics on G-banded metaphases and/or by fluorescence in situ hybridization (FISH). Measurable residual disease (MRD) negativity (sensitivity \(10^{-4}\)) was evaluated with 6- or 8-color flow cytometry at time of complete remission (CR) and at various time points during follow-up. We analyzed
patient characteristics at diagnosis and evaluated CR rates, overall survival (OS) and relapse-free survival (RFS). Survival curves were estimated using the Kaplan-Meier method and differences between groups were evaluated with the log-rank test. Univariate Cox proportional hazard models were used to estimate hazard ratios (HR). We performed a 4-month landmark analysis to evaluate the impact of HSCT in CR15. This study was approved by the Institutional Review Board at the MD Anderson Cancer Center and was conducted in accordance with the Declaration of Helsinki.

Results and Discussion

We identified 50 patients (5%) with ALL and KMT2A rearrangement. The most common abnormality was t(4;11)(q21;q23) identified in 42/50 (84%) patients. Eight (16%) patients had other KMT2A rearrangements: 4 (8%) had t(11;19)(q23;p13) – KMT2A-MLLT1 or KMT2A-ELL; 1 (2%) had t(9;11)(p21;q23) – KMT2A-MLLT3; 1 (2%) had t(11;15)(q32;q26) (unknown gene partner); and 2 (4%) had normal karyotype with cryptic KMT2A rearrangements identified by FISH (unknown gene partner). Fifteen (30%) patients had additional chromosomal abnormalities, with only i(7q) (3/50; 6%) and +X (2/50; 4%) identified in more than one case.

Patient characteristics are summarized in Table 1. All patients had B-cell ALL except one with T-cell ALL and t(4;11). The median age at diagnosis was 45 years (range, 18 – 78 years). The median white blood cell count (WBC) at diagnosis was 109 x 10^9/L (range, 0.5 – 1573.0) with more frequent hyperleukocytosis in patients with t(4;11).
CD19 was strongly expressed (≥ 70% of cells) in most patients (93%), whereas strong expression was less frequent for CD22 (35%). No patient had CD20 expression (≥ 20% of cells) and 1 (2%) patient had CD10 expression (≥ 20% of cells).

Most patients were treated with the Hyper-CVAD regimen (n=35)\textsuperscript{6}, or one of its variation (n=7)\textsuperscript{7-11}. Five patients were treated with the augmented Berlin-Frankfurt-Münster (BFM) regimen, two with other intensive regimens. One patient with t(4;11) died before starting treatment. The CR rate was 88% (44/50), 90% (38/42) among patients with t(4;11) and 75% (6/8) among patients with other KMT2A-rearrangements. Four (8%) patients died during induction and 1 (2%) patient with t(11;19) had refractory disease. The rate of MRD negativity at CR was 41% (12/29 evaluable patients), 41% (11/27) among patients with t(4;11), and 50% (1/2) among patients with other KMT2A-rearrangements. MRD negativity rate overall during follow-up was 76% (26/34 evaluable patients), 81% (25/31) among patients with t(4;11), and 33% (1/3) among patients with other KMT2A-rearrangements.

With a median follow-up of 63 months, 14 patients (28%) were alive at the last follow-up, 11 (22%) in CR1. The estimated 5-year OS and RFS rates were 18% (95% CI, 9 – 35%) and 15% (95% CI, 7 – 33%), respectively. There was no difference in OS (HR 1.08, p = 0.87) and RFS (HR 1.50, p = 0.41) according to the type of KMT2A abnormality (\textbf{Figure 1A-1B}). MRD positivity at CR trended to be associated with poor OS (HR 2.29, 95% CI 0.87 – 6.07, p = 0.09) and RFS (HR 2.25, 95% CI 0.94 – 5.38, p = 0.07) (\textbf{Figure 1C-1D}). Eighteen of the 44 patients (41%) achieving CR underwent
HSCT: 16 with t(4;11), of whom 5 (31%) remain alive in CR1; two with other KMT2A rearrangements, both alive, one in CR1. Among patients achieving CR who did not undergo HSCT, 5/22 (23%) with t(4;11) and 0/6 (0%) with other KMT2A rearrangements remain alive in CR1. The only patients with KMT2A rearrangements other than t(4;11) who remain alive are the two who underwent HSCT in CR1. Both had normal karyotype with KMT2A rearrangement identified by FISH. In a 4-month landmark analysis, the 5-year OS and RFS rates were 32% (95% CI, 14 – 70%) and 22% (95% CI, 8 – 58%) versus 11% (95% CI, 3 – 39%) and 11% (95% CI, 3 – 41%) among patients who underwent HSCT or not, respectively (HR for OS 0.53, p = 0.10; HR for RFS 0.54, p = 0.10; Figure 1E-1F). When selecting only patients diagnosed after 2010 to account for improvements in transplant-related morbidity and mortality over years, patients with KMT2A-rearranged ALL who underwent HSCT after 2010 had 5-year OS and RFS rates of 47% (95% CI, 21 – 100%) and 39% (95% CI, 17 – 94%), respectively, whereas no patient survived beyond 5 years among those who did not undergo HSCT (HR for OS 0.32, p = 0.08; HR for RFS 0.24, p = 0.03).

Blinatumomab or inotuzumab ozogamicin was administered as part of salvage treatment regimens in 8 patients with KMT2A-rearranged ALL who presented with relapsed or refractory disease. CR was achieved in 4/5 (80%) of patients receiving blinatumomab and in 3/4 (75%) of patients receiving inotuzumab ozogamicin. One patient sequentially received both drugs for two subsequent relapses and achieved CR both times. One additional patient in CR with MRD relapse achieved MRD eradication with blinatumomab.
*KMT2A*-rearranged ALL is a rare subgroup of ALL with poor outcome. The frequency of
*KMT2A* rearrangements of 5% in our study is slightly lower than what has been reported
by other groups. This difference might be related to different population
demographics at our institution in the same way Philadelphia chromosome-like ALL was
found to be more frequent at MD Anderson due to a higher proportion of patients with
Hispanic ethnicity. As reported previously, *KMT2A*-rearranged ALL was associated
with a higher WBC count at diagnosis in our cohort, especially among patients with
t(4;11). The outcome of ALL with *KMT2A* rearrangements is poor with a 5-year OS
and RFS rates of 17% and 15%, respectively, despite the achievement of a high CR
rate of 88%, similar to other subtypes of ALL. Only 1 (2%) patient had refractory
disease, which is lower than 11% reported in the UKALL/ECOG 2993 trial. The rate of
MRD negativity at CR was 41%, which is lower than rates observed overall in ALL and
explains partly the poor outcome in these patients. A recent report from our group
showed that MRD negativity and *KMT2A* rearrangements were independent factors
associated with event-free survival and OS. We confirm here that the MRD status is
relevant even in this adverse-risk ALL subgroup, although patients with *KMT2A-
rearranged ALL who achieve MRD negativity still had a poor outcome. There was no
difference in outcomes comparing patients with t(4;11) to other *KMT2A*-rearrangements.
This is in contrast to the study from the Group for Research on Adult Acute
Lymphoblastic Leukemia (GRAALL) in which other 11q23 abnormalities had similar
outcomes to normal karyotype. This discordance might be explained by the younger
age in the GRAALL cohort (median age 31 years for other *KMT2A*-r), different treatment
regimens, and a higher proportion of patients undergoing HSCT in CR1 (6/11, 55% for other KMT2A-r)\(^3\). Our findings are consistent with studies in children treated on the ALL97/99 trial\(^{15}\) and adults treated on the UKALL14 trial\(^{16}\). In both studies, t(4;11) and other KMT2A-rearranged ALL had similar prognoses.

Patients with KMT2A rearrangements benefited from HSCT in CR1. In our cohort, the 5-year OS and RFS rates were numerically higher among patients who underwent HSCT in CR1 (32% vs 11% for OS and 22% vs 11% for RFS) although these differences were not statistically significant likely due to the small number of patients. When considering patients diagnosed after 2010, the improvement in RFS was statistically significant with a 5-year RFS rate of 39% among patients who underwent HSCT in CR1 and no patient surviving beyond 4 years in those who did not. It is to mention that we could not eliminate the potential referral bias which could account for the more favorable outcomes in patients who have undergone HSCT. Nevertheless, even if a greater proportion of younger patients likely to have less comorbidities proceeded to HSCT in CR1, younger age was not associated with better outcomes in our study as opposed to HSCT. Altogether, the benefit of HSCT observed in our cohort is consistent with the study by the GRAALL, in which survival in patients with t(4;11) was worse when time was censored at HSCT in CR1\(^3\). Importantly, the only patients with other KMT2A-rearrangements in our study who remain alive were the two who underwent HSCT, suggesting that transplant is also beneficial in these patients.
We show that patients with *KMT2A*-rearranged ALL may benefit from blinatumomab and inotuzumab ozogamicin in the relapse or refractory setting. Menin inhibitors are also promising agents to target specifically *KMT2A*-rearranged leukemias by altering the interaction between menin and *KMT2A* fusion proteins.\textsuperscript{17, 18} Menin inhibitors have demonstrated impressive activity in patient-derived xenografts (PDX) models of *KMT2A*-rearranged leukemia\textsuperscript{17, 18} and early encouraging activity in ongoing clinical trials (SNDX-5613 and KO-539).\textsuperscript{19, 20}

In summary, our study confirms the poor prognosis of ALL with *KMT2A* rearrangements and the benefit of HSCT in CR1. MRD status is prognostic in this high-risk subgroup of ALL. The incorporation of new monoclonal antibodies (blinatumomab, inotuzumab ozogamicin) and other targeted therapies into the frontline regimens for ALL offers future hope for patients with *KMT2A*-rearranged ALL.\textsuperscript{21}
Data sharing statement

Original data will not be publicly available. For special inquiries, please contact ejabbour@mdanderson.org.

Authorship Contributions

GRC collected and analyzed the data. GRC and EJ wrote the manuscript. GT, CCY and JDK reviewed cytogenetics and pathology of cases. EJ and other authors treated patients included in this study and revised the manuscript.

Disclosure of Conflicts of Interest

G.R.-C received consulting fees from Astellas and Taiho Pharma. H.K. received research grants and honoraria from AbbVie, Agios, Amgen, Immunogen and Pfizer; received research grants from Ariad, Astex, Bristol-Myer-Squibb, Cyclacel, Daiichy-Sankyo, Jazz Pharma, and Novartis; received honoraria from Takeda and attended advisory board for Actinium. G.C.I. received research funding from Celgene, Kura Oncology, Syndax and Novartis; served on an advisory board for Novartis, and received consulting fees from Kura Oncology. N.J. received research grants and consulting fees from Servier, Pharmacyclics, AstraZeneca, Genentech, Verastem, Pfizer, AbbVie, ADC Therapeutics, Precision Biosciences and Adaptive Biotechnologies; received research grants from Bristol-Myer-Squibb, Celgene, Seattle Genetics and Incyte; and received consulting fees from Janssen. N.J.S. received research grants from Takeda and Astellas and consulting fees from Takeda, AstraZeneca and Amgen. C.D.D. received research grants and consulting fees from AbbVie and Celgene; received consulting fees from Agios, Jazz, Syros and Daiichi-Sankyo; and attended scientific advisory board for Notable Labs. K.T. received consulting fees from Glaxo-Smith-Kline, Symbio Pharmaceuticals and Celgene and received honoraria from Dava Oncology. M.K. received research grants and consulting fees from AbbVie, Genentech, F. Hoffman La-Roche and Stemline Therapeutics; received consulting fees from Amgen, Forty-Seven and Kisoji; received research grants from Eli Lilly, Cellectis, Calithera, Ablynx, Agios, Ascentage and Astra Zeneca; received stock options from Reata Pharmaceutical and Kisoji and received royalties from Reata Pharmaceuticals. N.G.D. received research grants, consulting fees and honoraria from Pfizer, Bristol-Myer-Squibb, Novartis, Incyte, Immunogen, Astellas and AbbVie; received research grants and consulting fees from Daiichi-Sankyo, Karyopharm, Sunesis; received consulting fees and honoraria from Otsuka; received research grants only from Servier, Genentech, NOHLA, Glycomimetics, Sobi, Hanmi and Forty Seven; and received consulting fees only from Celgene, Jazz and Agios. E.J. received research grants and consulting fees from AbbVie, Adaptive Biotechnologies, Amgen, Astellas, Bristol-Myer-Squibb, Daiichi Sankyo, Novartis, Pfizer, and Takeda. G.T., C.C.Y., J.D.K., F.G.H., F.R., T.K., G.G-M, R.G., S.O’B. have no conflict of interest to disclose.
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Table 1. Characteristics of the Patients at Baseline

| Characteristic                  | Total (N = 50) | t(4;11) (N = 42) | Other KMT2A-r (N = 8) | Non KMT2-r (N = 1052) |
|--------------------------------|----------------|------------------|----------------------|-----------------------|
| **Age (years)**                |                |                  |                      |                       |
| Age < 40 years-old             | 21 (42)        | 17 (40)          | 4 (50)               | 451 (43)              |
| Gender (Male)                  | 19 (38)        | 16 (38)          | 3 (38)               | 613 (58)              |
| **Hematologic parameters**     |                |                  |                      |                       |
| WBC (x 10^9/L)                 | 109.0 [0.5 – 1573.0] | 111.8 [0.5 – 1573.0] | 37.0 [4.6 – 423.1] | 8.0 [0.2-1037]       |
| WBC ≥ 30 x 10^9/L              | 39 (78)        | 35 (83)          | 4 (50)               | 303 (29)              |
| WBC ≥ 100 x 10^9/L             | 29 (58)        | 26 (62)          | 3 (38)               | 132 (13)              |
| Hb (g/dL)                      | 9.4 [3.6 – 16.5] | 9.4 [3.6 – 13.5] | 9.0 [5.9 – 16.5]     | 9.3 [3.5-16.4]        |
| Plt (x 10^9/L)                 | 43 [6 – 442]   | 43 [7 – 442]     | 50 [6 – 191]         | 45 [0-626]            |
| **Cell lineage**               |                |                  |                      |                       |
| B-cell ALL                     | 44/45 (98)     | 38/39 (97)       | 6/6 (100)            | 913 (87)              |
| T-cell ALL                     | 1/45 (2)       | 1/39 (3)         | 0/6 (0)              | 138 (13)              |
| **Immunophenotype***           |                |                  |                      |                       |
| CD19+ (≥ 70% cells)            | 40/43 (93)     | 36/38 (95)       | 4/5 (80)             | 806/971 (83)          |
| CD10+ (≥ 20% cells)            | 1/47 (2)       | 1/41 (2)         | 0/6 (0)              | 414/561 (74)          |
| CD20+ (≥ 20% cells)            | 0/45 (0)       | 0/39 (0)         | 0/6 (0)              | 467/944 (49)          |
| CD22+ (≥ 70% cells)            | 13/37 (35)     | 13/33 (83)       | 0/4 (0)              | 620/873 (71)          |
| **Additional abnormalities**   |                |                  |                      |                       |
| Overall                        | 15 (30)        | 12 (26)          | 3 (38)               | NA                    |
| Isochromosome 7q               | 3 (6)          | 3 (7)            | 0 (0)                | NA                    |
| + X                            | 2 (4)          | 2 (5)            | 0 (0)                | NA                    |

Numbers with percentages in parentheses. Medians with ranges in brackets.
Abbreviations: WBC, white blood cell count; Hb, hemoglobin; Plt, platelets.
* Immunophenotype data is missing for some markers in some patients (7 missing for CD19, 3 missing for CD10, 5 missing for CD20, 13 missing for CD22)
Figure 1. Clinical outcomes of patients with \textit{KMT2A}-rearranged ALL. OS (A) and RFS (B) according to the type of \textit{KMT2A} rearrangement. OS (C) and RFS (D) according to MRD status at time of CR. OS (E) and RFS (F) with landmark analysis for HSCT in CR1.

Abbreviations: OS, overall survival; RFS, relapse-free survival; MRD, measurable residual disease; HSCT, allogeneic hematopoietic stem cell transplantation; CR1, first complete remission.