STIMULUS REPORT

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Outcomes of acute lymphoblastic leukemia with *KMT2A* (*MLL*) rearrangement: the MD Anderson experience

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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 HSCT in first remission.

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 transplantation (HSCT) is unclear. We reviewed adult patients with ALL treated at our institution from 1984 to 2019 and identified 50 out of 1102 (5%) with KMT2A rearrangement, including 42 (84%) with t(4;11)/KMT2A-AFF1 and 8 (16%) with other gene partners. The median age was 45 years (range, 18-78 years); median white blood cell count was 109.0 3 109/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% confidence interval [CI], 9% to 35%), with no difference between t(4;11) and other KMT2A rearrangements (P 5 .87). In a 4-month landmark analysis, the 5-year OS rate was 32% (95% CI, 14% to 70%) in patients who underwent HSCT vs 11% (95% CI, 3-39) in others (P 5 .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, and 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 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 fluorescence in situ hybridization (FISH). Measurable residual disease (MRD) negativity (sensitivity 10^{-4}) was evaluated with 6- or 8-color flow

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cytometry at time of 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 (HRs). We performed a 4-month landmark analysis to evaluate the impact of HSCT in CR1.[5] 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 out of 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)(q23;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 >1 case.

Patient characteristics are summarized in Table 1. All patients had B-cell ALL, except 1 patient 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 (WBC) count at diagnosis was 109 × 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 patient (2%) had CD10 expression (≥20% of cells).

Most patients were treated with the hyper-CVAD regimen (hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; n = 35),[6] or one of its variations (n = 7).[7-11] Five patients were treated with the augmented Berlin-Frankfurt-Münster regimen, 2 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 patient (2%) 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. The 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% confidence interval [CI], 9% to 35%) and 15% (95% CI, 7% to 33%), respectively. There was no difference in OS (HR, 1.08; $P = .87$) and RFS (HR, 1.50; $P = .41$) according to the type of *KMT2A* abnormality (Figure 1A-B). MRD positivity at CR trended to be associated with poor OS (HR, 2.29; 95% CI, 0.87-6.07; $P = .09$) and RFS (HR, 2.25; 95% CI, 0.94-5.38; $P = .07$)

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 (y)	45 [18-78]	45 [18-74]	42 [19-78]	44 [18-85]
<40 y	21 (42)	17 (40)	4 (50)	451 (43)
Gender (male)	19 (38)	16 (38)	3 (38)	613 (58)
Hematologic parameters				
WBC (×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 ×10^9/L	39 (78)	35 (83)	4 (50)	303 (29)
WBC ≥ 100 ×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 (×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

Data are presented as numbers with percentages in parentheses or medians with ranges in brackets.
Hb, hemoglobin; *KMT2A*-r, *KMT2A* rearranged/rearrangement; Plt, platelets.
*Immunophenotype data are missing for some markers in some patients (7 are missing for CD19, 3 are missing for CD10, 5 are missing for CD20, and 13 are missing for CD22)

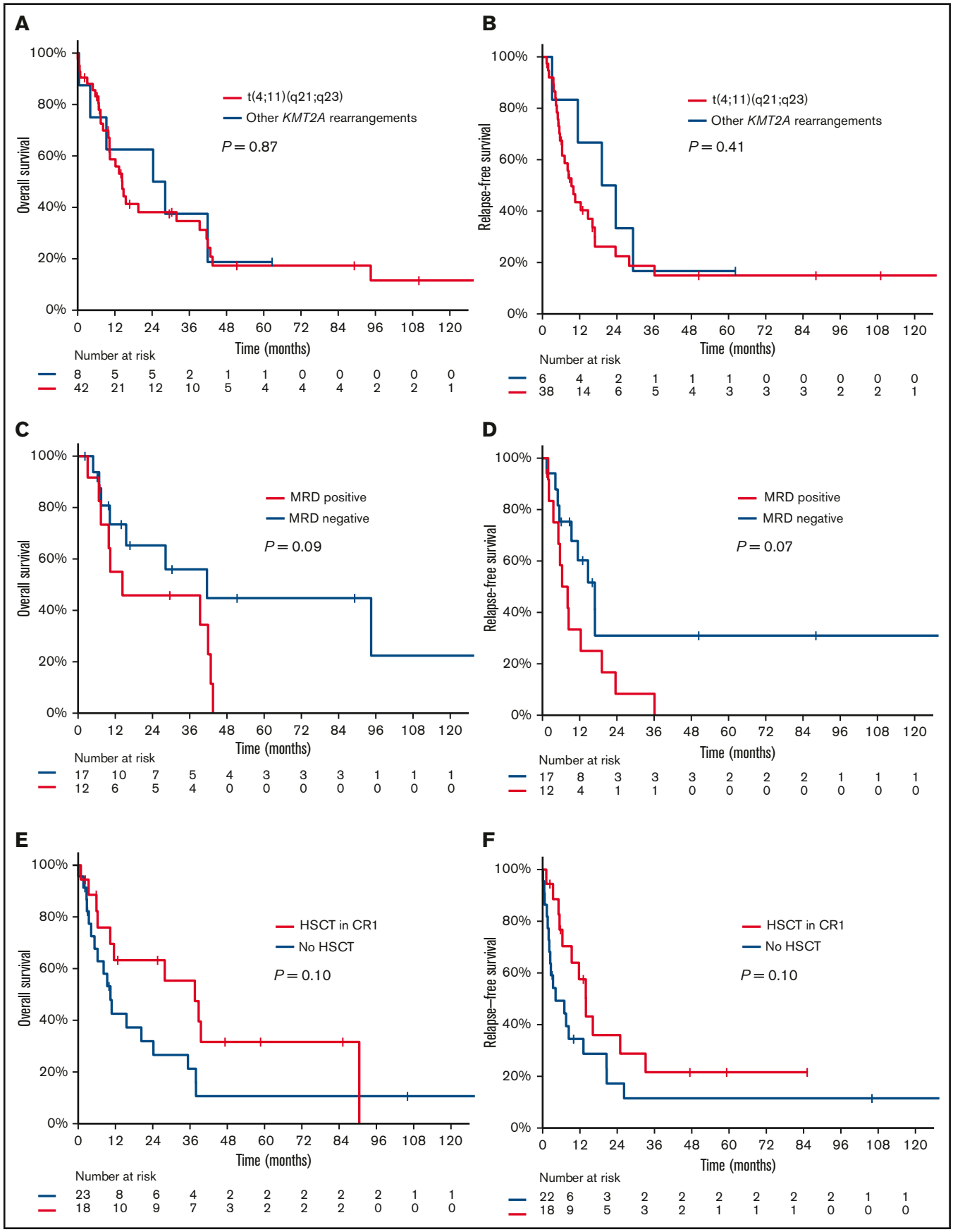

Figure 1. Clinical outcomes of patients with *KMT2A*-rearranged ALL. OS (A) and RFS (B) according to the type of *KMT2A* rearrangement. OS (C) and RFS (D) according to MRD status at time of CR. OS (E) and RFS (F) with landmark analysis for HSCT in CR1.

(Figure 1C-D). Eighteen of the 44 patients (41%) achieving CR underwent HSCT, including 16 with t(4;11), of whom 5 (31%) remain alive in CR1, and 2 patients with other *KMT2A* rearrangements (both alive, with 1 patient in CR1). Among patients achieving CR who did not undergo HSCT, 5 out of 22 patients (23%) with t(4;11) and 0 out of 6 patients (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 2 patients 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% to 70%) and 22% (95% CI, 8% to 58%) vs 11% (95% CI, 3% to 39%) and 11% (95% CI, 3% to 41%) among patients who underwent HSCT or not, respectively (HR for OS: 0.53, $P = .10$; HR for RFS: 0.54, $P = .10$; Figure 1E-F). When selecting only patients diagnosed after 2010 to account for improvements in transplant-related morbidity and mortality over the years, patients with *KMT2A*-rearranged ALL who underwent HSCT after 2010 had 5-year OS and RFS rates of 47% (95% CI, 21% to 100%) and 39% (95% CI, 17% to 94%), respectively, whereas no patient survived beyond 5 years among those who did not undergo HSCT (HR for OS: 0.32, $P = .08$; HR for RFS: 0.24, $P = .03$).

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 out of 5 patients (80%) receiving blinatumomab and in 3 out of 4 patients (75%) receiving inotuzumab ozogamicin. One patient sequentially received both drugs for 2 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.[1,3] 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.[12] 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).[1,3] 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 patient (2%) had refractory disease, which is lower than 11% reported in the UKALL/ECOG 2993 trial.[1] 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.[2,13,14] A recent report from our group showed that MRD negativity and *KMT2A* rearrangements were independent factors associated with event-free survival and OS.[14] 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.[3] This discordance might be explained by the younger age in the GRAALL cohort (median age 31 years for other *KMT2A*-rearrangements), 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 worth mentioning 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 GRAALL study, 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 2 patients 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[17,18] Menin inhibitors have demonstrated impressive activity in patient-derived xenograft models of *KMT2A*-rearranged leukemia[17,18] and early encouraging activity in ongoing clinical trials (SNDX-5613 and KO-539).[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 and inotuzumab ozogamicin) and other targeted therapies into the frontline regimens for ALL offers future hope for patients with *KMT2A*-rearranged ALL.[21]

Authorship

Contribution: G.R.-C. collected and analyzed the data; G.R.-C. and E.J. wrote the manuscript; G.T., C.C.Y., and J.D.K. reviewed cytogenetics and pathology of cases; and E.J. and other authors treated patients included in this study and revised the manuscript.

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