Therapeutic effect of allogeneic stem cell transplantation in acute myeloid leukemia patients with epigenetic modifier gene mutations

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Abstract

Background

Epigenetic modifier gene mutations (EMM) have been reported to be associated with poor prognosis in acute myeloid leukemia (AML). Whether allogeneic stem cell transplantation (allo-HSCT) can improve outcomes in this patients remains unknown.

Material/Methods:

This study retrospectively collected clinical information of 353 AML patients with gene mutations detected by next-generation sequencing (NGS) and analyzed the therapeutic effect of allogeneic stem cell transplantation in acute myeloid leukemia patients with epigenetic modifier gene mutations.

Results

EMM-positive patients tended to have inferior OS compared with EMM-negative patients (p = 0.065, HR = 1.343, 95%CI: 0.981–1.838), EMM-positive patients had inferior LFS (p = 0.031, HR = 1.385, 95%CI: 1.030–1.863). In EMM-positive patients, multivariate analysis showed that patients who received allo-HSCT had a superior OS (yes vs. no, p < 0.001, HR = 0.213, 95%CI: 0.134–0.339, Table 3) and LFS (yes vs. no, p < 0.001, HR = 0.303, 95%CI: 0.199–0.461, Table 3) compared with patients who did not receive allo-HSCT. A total of 220 patients received allo-HSCT in all patients. Univariate analysis in patients undergoing allo-HSCT showed that EMM was not a risk factor for OS (EMM-positive vs. EMM-negative, p = 0.470, HR = 1.192, 95%CI: 0.740–1.920) and LFS (EMM-positive vs. EMM-negative, p = 0.323, HR = 1.235, 95%CI: 0.813–1.876).

Conclusion

EMM tended to be a poor risk factor for OS and was a poor risk factor for LFS in our cohort. Allo-HSCT might improve the OS and LFS of EMM-positive patients.

Background

Acute myeloid leukemia is the most common adult acute leukemia of highly heterogeneous. Over the past years, anthracycline-based regimen remained the standard induction therapy, achieving 60%-80% complete remission rates (CRR) in newly diagnosed acute myeloid leukemia (AML) [1, 2]. However, the majority of patients still suffer from relapsed or refractory diseases [3–6]. The prognosis of these patients is dismal. Allogeneic stem cell transplantation (allo-HSCT) is one of the most effective therapies in AML. Early use of allo-HSCT for poor-risk patients at the first complete remission (CR) can significantly improve the survival of these patients [7].

Epigenetic modifier gene mutations (EMM), mainly including DNMT3A [8], TET2 [9], IDH1, and IDH2 [10], have been reported to be associated with poor prognosis in AML. Some studies show that decitabine

could benefit EMM-positive AML patients with intermediate-risk karyotypes [11]. Compared with patients without DNMT3A mutations, patients harboring DNMT3A mutations responded well to decitabine in acute myeloid leukemia [12]. Others show that allo-HSCT could improve the survival of patients with DNMT3A mutations in cytogenetically normal adult AML and with DNA-methylation regulatory gene mutations in AML [13, 14]. Nonetheless, fewer studies explored the therapeutic effect of allo-HSCT in patients with combined mutations of methylation and acetylation regulatory genes. In this article, we aimed to study whether there was an association between the therapeutic effect of allo-HSCT and epigenetic modifier gene mutations (EMM). We then explored whether different induction regimens could influence the survival of EMM-positive patients undergoing allo-HSCT. We also analyzed the prognostic factors before transplant in patients undergoing allo-HSCT.

Materials and Methods

Patients

A total of 353 AML patients were involved in this retrospective study. Patients with acute promyelocytic leukemia were excluded. Bone marrow (BM) or peripheral blood (PB) samples were obtained in patients who received treatment in Chinese PLA General Hospital between August 2008 and November 2020 before treatment. This study was approved by the Ethics Committee of the General Hospital of the Chinese People's Liberation Army, following the Declaration of Helsinki. The diagnosis and classification of patients were performed according to French-American-British (FAB) and World Health Organization (WHO). NCCN risk stratifications were performed based on NCCN guidelines 2021 [15].

Treatment

In our study, a total of 116 patients received a DCAG regimen as an induction regimen, and 237 patients received a conventional "3 + 7" regimen as an induction regimen. Treatment options were based on the patient's wishes and the physician's evaluation. The DCAG standard regimen included decitabine (DAC) 20 mg/m^2, intravenous drip (VD) Day 1-5; cytarabine 100 or 200 mg/m^2 every 12 hours, VD Day 1–5; aclarubicin 10 mg/m^2/day, intravenous injection (IV) Day 1–5, and G-CSF 300 μg/day subcutaneously from Day 0 to neutrophil recovery. DCAG regimen for elderly patients included decitabine 20 mg/m^2, intravenous drip (VD) Day 1–5; cytarabine 10 or 20 mg/m^2 every 12 hours, VD Day 1–5; aclarubicin 10 mg/m^2/day, IV Day 1–5, and G-CSF 300 μg/day subcutaneously from Day 0 to neutrophil recovery. The conventional "3 + 7" regimen included one of the anthracyclines (daunorubicin or idarubicin) or mitoxantrone or homoharringtonine for 3 days, and cytarabine for 7 days, as previously described [16, 11]. After induction therapy, 220 out of 353 patients received allo-HSCT. The number of patients achieving first CR (CR1), second CR (CR2), partial remission (PR), non-remission (NR), and relapsed before transplantation was 191 (86.8%), 10 (4.6%), 6 (2.7%), 4 (1.8%), and 9 (4.1), respectively (Table 1).

Table 1
Clinical characteristics of 353 patients.

Characteristic	No. (%)
Age, y, median (range)	42 (10–78)
< 60y	307 (87.0)
≥ 60y	46 (13.0)
Gender	
Female	142 (40.2)
Male	211 (59.8)
Extramedullary infiltration	
No	331 (93.8)
Yes	22 (6.2)
Median WBC, $\times 10^9$/L (range)	10.84 (0.25-405.13)
<10×10^9/L	168 (47.6)
≥10×10^9/L	185 (52.4)
Median Hb, g/L (range) [1]	83 (26–161)
Median PLT, $\times 10^9$/L (range) [1]	43 (3-924)
Median BM blast, % (range)	59.2 (20.0–96.0)
<50%	142 (40.2)
≥50%	211 (59.8)
Origin of disease	
De novo AML	323 (91.5)
Secondary AML	30 (8.5)
FAB classification	
M0	1 (0.3)

WBC, white blood cells; Hb, hemoglobin; PLT, platelet; BM, bone marrow; FAB, French–American–British; NCCN, National Comprehensive Cancer Network; Allo-HSCT, allogeneic hematopoietic stem cell transplantation; CR1, first complete remission; CR2, second complete remission; PR, partial remission; NR, non-remission; EMM +, epigenetic modifier gene mutation-positive.

[1] Information of one patient was missing

Characteristic	No. (%)
M1	7 (2.0)
M2	116 (32.9)
M4	70 (19.8)
M5	81 (22.9)
M6	6 (1.7)
M7	1 (0.3)
undefined	71 (20.1)
NCCN risk stratification	
Favorable	143 (40.5)
Intermediate	86 (24.4)
Poor	124 (35.1)
Types of induction therap	
3 + 7 regimen	237 (67.1)
DCAG regimen	116 (32.9)
Allo-HSCT	
No	133 (37.7)
Yes	220 (62.3)
Disease status before transplantation	
CR1	191 (86.8)
CR2	10 (4.6)
PR	6 (2.7)
NR	4 (1.8)
relapse	9 (4.1)
EMM +	

WBC, white blood cells; Hb, hemoglobin; PLT, platelet; BM, bone marrow; FAB, French–American–British; NCCN, National Comprehensive Cancer Network; Allo-HSCT, allogeneic hematopoietic stem cell transplantation; CR1, first complete remission; CR2, second complete remission; PR, partial remission; NR, non-remission; EMM +, epigenetic modifier gene mutation-positive.

[1] Information of one patient was missing

Characteristic	No. (%)
No	192 (54.4)
Yes	161 (45.6)
WBC, white blood cells; Hb, hemoglobin; PLT, platelet; BM, bone marrow; FAB, French–American–British; NCCN, National Comprehensive Cancer Network; Allo-HSCT, allogeneic hematopoietic stem cell transplantation; CR1, first complete remission; CR2, second complete remission; PR, partial remission; NR, non-remission; EMM +, epigenetic modifier gene mutation-positive.	
[1] Information of one patient was missing	

Prognostic endpoints

The primary endpoints were overall survival (OS) and leukemia-free survival (LFS). The OS was defined as the time from diagnosis to death from any cause or the last follow-up (July 20th ,2021). The LFS was defined as the time from diagnosis to relapse or death or the last follow-up. LFS of refractory patients was defined as zero. CR, PR, and NR were defined according to NCCN. Overall response rate (ORR) included patients who obtained CR or PR. Three patients were lost during follow-up. The median follow-up was 23.63 months (range: 0.40-145.80 months).

Next-generation sequencing

Genomic DNA was isolated from bone marrow or peripheral blood samples. Mutation detection was performed using a targeted capture deep sequencing with next-generation sequencing at Acornmed Biotechnology Co. Ltd (Tianjin, China) (Supplementary Table S1). NovaSeq instrument (Illumina) was used to sequence multiplex libraries. Then, trimmed reads were aligned by using Burrows-Wheeler Alignment (BWA, version 0.7.12). PCR duplicates were marked by using the MarkDuplicates tool from Picard. The BWA data was then realigned and recalibrated by using IndelRealigner and BaseRecalibrator from Genome Analysis Toolkit (GATK; version 3.8). Variants, including the SNVs and Indels, were called by using mutect2. At last, ANNOVAR software was used to annotate variants. Patients harboring ≥ 1 mutation in genes with epigenetically modified functions, including mutated DNMT3A, IDH1, IDH2, TET2, ASXL1, KMT2C, EZH2, SETD2, CREBBP, EP300, and KDM6A, were defined as epigenetic modifier gene mutation-positive (EMM-positive) group. Patients without the aforementioned mutated genes were assigned to the epigenetic modifier gene mutation-negative (EMM-negative) group.

Statistical analysis

Statistical analysis was performed by using SPSS 24.0 and GraphPad Prism 8.0.2 software. Mutation frequency was calculated by dividing the number of mutations by sample size. Continuous variables (age, white blood cell [ABC] count, hemoglobin level, platelet count, percentage of bone marrow [BM] blast) were exhibited as median (range). Mann-Whitney U test was used to compare these variables. Chi-square test was exerted to compare categorical variables (age, gender, extramedullary infiltration, WBC count, percentage of BM blast, origin of disease, FAB classification, NCCN risk stratification, types of induction therapy, EMM, response rate). For the expected count of an event < 5 or a total number of

patients < 40, fisher's exact test was used. The COX proportional hazard model was used to perform univariate and multivariate analysis of the OS and LFS, a stepwise backward procedure selection model was used for extracting independent factors in multivariate analysis. Parameters with sample size > 2 were included in univariate analysis. Parameters with a *p*-value < 0.1 were included in the multivariate analysis. Kaplan-Meier (K-M) analysis was used to compare OS and LFS between two groups and among five groups. Log-rank test was used to calculate the *p*-value. A two-sided $p < 0.05$ was considered statistically significant.

Results

Gene mutation profile in AML patients

A total of 812 mutations in 59 genes were discovered in 309 of 353 patients. Gene mutation profile in 353 patients were shown in Fig. 1. Genes with mutation frequency > 10% were biCEBPA (20.1%), NRAS (17.6%), DNMT3A (15.6%), NPM1 (14.7%), FLT3-ITD (14.4%), and TET2 (11.0%) (Supplementary Figure S1a). All mutated genes were grouped into eight different functional pathways, including EMM-positive group which harbored eleven mutated genes (Fig. 1). In EMM-positive patients, 161 (45.6%) cases harbored mutated DNMT3A (34.2%), TET2 (24.2%), ASXL1 (20.5%), IDH2 (18.6%), IDH1 (14.3%), KDM6A (6.2%), EZH2 (5.6%), SETD2 (3.1%), KMT2C (2.5%), EP300 (1.9%), and CREBBP (1.2%) (Supplementary Figure S1b). In EMM-negative patients, genes with mutation frequency > 10% were biCEBPA (23.4%), NRAS (15.1%), FLT3-ITD (14.1%), and WT1 (10.4%) (Supplementary Figure S1c).

Clinical data of all patients

A total of 353 de novo AML patients were included in our study. Clinical characteristics of all patients were listed in Table 1. Patients with or without EMM were assigned to the EMM-positive group or EMM-negative group, respectively. Patients who were EMM-positive had a higher proportion of elderly patients (19.3% *vs.* 7.8%, $p = 0.001$, Supplementary Table S2) and a lower proportion of extramedullary infiltration (3.1% *vs.* 8.9%, $p = 0.026$) and elevated WBC counts (46.6% *vs.* 57.3%, $p = 0.045$) than patients who were EMM-negative. The proportion of patients receiving the DCAG regimen in EMM-positive group was higher than that in EMM-negative group (41.0% *vs.* 26.0%, $p = 0.003$, Supplementary Table S2). There were no differences in the distribution of gender, Hb counts, PLT counts, percentage of BM blast, origin of disease, FAB classification, NCCN risk stratification, and allo-HSCT between the two groups (Supplementary Table S2). In EMM-positive group, there were 51, 8, 13 and 11 patients who received "3 + 7" regimen followed by allo-HSCT, "3 + 7" regimen, DCAG regimen followed by allo-HSCT and DCAG regimen achieving CR, respectively (Supplementary Table S3). In EMM-negative group, there were 81, 12, 11 and 19 patients who received "3 + 7" regimen followed by allo-HSCT, "3 + 7" regimen, DCAG regimen followed by allo-HSCT and DCAG regimen achieving CR, respectively (Supplementary Table S4).

Prognostic factors for OS and LFS in 353 patients

Univariate analysis of the OS and LFS in all patients showed that EMM was a poor risk factor for OS and LFS. Other risk factors included age ≥ 60y, extramedullary infiltration, NCCN risk stratification (Intermediate vs. Favorable, Poor vs. Favorable), types of induction regimen (DCAG vs. 3 + 7 regimen), mutated KRAS, mutated SF3B1 were poor risk factors of OS (Table 2). Allo-HSCT was a favorable risk factor of OS ($p < 0.001$, HR = 0.239, 95%CI: 0.175–0.326). Risk factors included age ≥ 60y, extramedullary infiltration, NCCN risk stratification (Intermediate vs. Favorable, Poor vs. Favorable), types of induction regimen (DCAG vs. 3 + 7 regimen), mutated SETBP1, mutated SF3B1 were poor risks factor of LFS (Table 2). Mutated KRAS tended to have a poor prognosis in LFS ($p = 0.0550$, HR = 1.896, 95%CI: 1.000-3.593). Allo-HSCT was a favorable risk factor of OS ($p < 0.001$, HR = 0.324, 95%CI: 0.242–0.434, Table 2).

Table 2
Univariate and multivariate analysis of 353 patients.

	Univariate analysis			Multivariate analysis		
	p-value	HR	95% *CI*	*p*-value	HR	95% *CI*
OS						
Age (≥ 60y vs. <60y)	< 0.001	2.998	2.068–4.347			
Extramedullary infiltration	0.006	2.077	1.239–3.481	< 0.001	2.633	1.550–4.474
NCCN	< 0.001			< 0.001		
Intermediate vs. Favorable	0.008	1.728	1.150–2.597	< 0.001	2.379	1.571–3.603
Poor vs. Favorable	< 0.001	2.229	1.560–3.185	< 0.001	2.320	1.619–3.325
Types of induction regimen						
DCAG vs. 3 + 7 regimen	< 0.001	1.824	1.341–2.482			
Allo-HSCT	< 0.001	0.239	0.175–0.326	< 0.001	0.224	0.162–0.308
Mutated KRAS	0.006	2.445	1.285–4.650			
Mutated SF3B1	0.029	3.034	1.118–8.230			
EMM (+) vs. EMM (-)	0.023	1.385	1.047–1.833	0.065	1.343	0.981–1.838
LFS						
Age (≥ 60y vs. <60y)	< 0.001	2.769	1.924–3.985			
Extramedullary infiltration	0.002	2.174	1.316–3.591	< 0.001	2.563	1.538–4.272
NCCN	0.001			< 0.001		
Intermediate vs. Favorable	0.050	1.463	1.000-2.141	0.005	1.756	1.186–2.601
Poor vs. Favorable	< 0.001	1.939	1.389–2.707	< 0.001	2.034	1.450–2.853
Types of induction regimen						
DCAG vs. 3 + 7 regimen	0.001	1.665	1.242–2.232			
Allo-HSCT	< 0.001	0.324	0.242–0.434	< 0.001	0.313	0.231–0.423
Mutated SETBP1	0.046	2.472	1.015–6.021	0.009	3.418	1.365–8.559
Mutated KRAS	0.050	1.896	1.000-3.593			
Mutated SF3B1	0.008	3.897	1.429–10.624	0.057	2.718	0.971–7.606

NCCN, National Comprehensive Cancer Network; Allo-HSCT, allogeneic hematopoietic stem cell transplantation; EMM +, epigenetic modifier gene mutation-positive; EMM −, epigenetic modifier gene mutation-negative.

	Univariate analysis			Multivariate analysis		
	p-value	HR	95% *CI*	*p*-value	HR	95% *CI*
EMM (+) vs. EMM (-)	0.009	1.468	1.101–1.957	0.031	1.385	1.030–1.863

NCCN, National Comprehensive Cancer Network; Allo-HSCT, allogeneic hematopoietic stem cell transplantation; EMM +, epigenetic modifier gene mutation-positive; EMM −, epigenetic modifier gene mutation-negative.

Multivariate analysis showed that EMM-positive patients tended to have inferior OS (EMM-positive *vs.* EMM-negative, $p = 0.065$, HR = 1.343, 95%CI: 0.981–1.838, Table 2) and had inferior LFS (EMM-positive *vs.* EMM-negative, $p = 0.031$, HR = 1.385, 95%CI: 1.030–1.863, Table 2) compared with EMM-negative patients. Allo-HSCT was an independent risk factor for OS and LFS (OS: yes *vs.* no, $p < 0.001$, HR = 0.224, 95%CI: 0.162–0.308; LFS: yes *vs.* no, $p < 0.001$, HR = 0.313, 95%CI: 0.231–0.423). Other independent risk factors for OS were extramedullary infiltration (yes *vs.* no, $p < 0.001$, HR = 2.633, 95%CI: 1.550–4.474), NCCN risk stratification (intermediate *vs.* favorable, $p < 0.001$, HR = 2.379, 95%CI: 1.571–3.603; poor *vs.* favorable, $p < 0.001$, HR = 2.320, 95%CI: 1.619–3.325). Other independent risk factors affecting LFS were extramedullary infiltration (yes *vs.* no, $p < 0.001$, HR = 2.563, 95%CI: 1.538–4.272), NCCN risk stratification (intermediate *vs.* favorable, $p = 0.005$, HR = 1.756, 95%CI: 1.186–2.601; poor *vs.* favorable, $p < 0.001$, HR = 2.034, 95%CI: 1.450–2.853), and mutated SETBP1 (yes *vs.* no, $p = 0.009$, HR = 3.418, 95%CI: 1.365–8.559) (Table 2).

Allo-HSCT can reverse the poor prognosis of patients with EMM regardless of induction regimens

In EMM-positive patients, multivariate analysis showed that patients who received allo-HSCT had a superior OS (yes *vs.* no, $p < 0.001$, HR = 0.213, 95%CI: 0.134–0.339, Table 3) and LFS (yes *vs.* no, $p < 0.001$, HR = 0.303, 95%CI: 0.199–0.461, Table 3) compared with patients who did not receive allo-HSCT. Other independent risk factors for OS and LFS were origin of disease (secondary vs. de novo, OS: $p = 0.002$, HR = 3.368, 95%CI: 1.563–7.257; LFS: $p = 0.002$, HR = 3.288, 95%CI: 1.528–7.072). In patients undergoing allo-HSCT, K-M analysis showed that the two-year OS and LFS rate of patients receiving the DCAG regimen were similar to that of patients receiving the “3 + 7” regimen (the DCAG regimen followed by allo-HSCT group *vs.* the “3 + 7” regimen followed by allo-HSCT group, two-year OS, 71.43% *vs.* 72.64%, $p = 0.677$; two-year LFS, 52.44% *vs.* 63.43%, $p = 0.542$, Fig. 2A-B).

Table 3
Univariate and multivariate analysis of patients who were EMM-positive.

	Univariate analysis			Multivariate analysis		
	p-value	HR	95% *CI*	*p*-value	HR	95% *CI*
OS						
Age (≥ 60y vs. <60y)	< 0.001	2.988	1.876–4.757			
Extramedullary infiltration	0.052	2.722	0.990–7.482			
Origin of disease						
Secondary vs. de novo	< 0.001	4.649	2.220–9.733	0.002	3.368	1.563–7.257
NCCN	0.019			0.098		
Intermediate vs. Favorable	0.189	1.488	0.822–2.695	0.081	1.731	0.934–3.207
Poor vs. Favorable	0.005	2.020	1.238–3.296	0.049	1.651	1.002–2.721
Types of induction regimen						
DCAG vs. 3 + 7 regimen	0.002	1.969	1.285–3.017			
Allo-HSCT	< 0.001	0.214	0.136–0.336	< 0.001	0.213	0.134–0.339
Mutated KRAS	0.081	2.244	0.906–5.560			
Mutated JAK2	0.058	3.993	0.955–16.694			
Mutated U2AF1	0.037	2.622	1.059–6.489			
LFS						
Age (≥ 60y vs. <60y)	< 0.001	2.391	1.515–3.771			
Origin of disease						
Secondary vs. de novo	0.001	3.748	1.778–7.901	0.002	3.288	1.528–7.072
NCCN	0.088					
Intermediate vs. Favorable	0.449	1.239	0.712–2.155			
Poor vs. Favorable	0.029	1.671	1.055–2.645			
Types of induction regimen						
DCAG vs. 3 + 7 regimen	0.002	1.894	1.264–2.839			
Allo-HSCT	< 0.001	0.297	0.196–0.450	< 0.001	0.303	0.199–0.461

NCCN, National Comprehensive Cancer Network; Allo-HSCT, allogeneic hematopoietic stem cell transplantation. CRR, complete remission rate; ORR, overall remission rate.

	Univariate analysis			Multivariate analysis		
	p-value	HR	95% *CI*	*p*-value	HR	95% *CI*
Mutated SF3B1	0.095	5.477	0.746–40.209			

NCCN, National Comprehensive Cancer Network; Allo-HSCT, allogeneic hematopoietic stem cell transplantation. CRR, complete remission rate; ORR, overall remission rate.

Prognostic factors before transplant in patients undergoing allo-HSCT

Univariate analysis in patients undergoing allo-HSCT showed that EMM was not a risk factor for OS (EMM-positive vs. EMM-negative, $p = 0.470$, HR = 1.192, 95%CI: 0.740–1.920) and LFS (EMM-positive vs. EMM-negative, $p = 0.323$, HR = 1.235, 95%CI: 0.813–1.876) (Table 4, Fig. 2C-D). Multivariate analysis of OS showed that patients with non-remission status before allo-HSCT was an adverse prognostic factor in patients undergoing allo-HSCT (NR vs. CR1, $p = 0.021$, HR = 2.168, 95%CI: 1.123–4.188) (Table 4, Fig. 2E). Other independent adverse risk factor for OS was mutated KRAS (yes *vs.* no, $p = 0.016$, HR = 4.230, 95%CI: 1.606–17.301). Multivariate analysis of LFS showed that patients achieving CR1 before allo-HSCT had superior LFS compared with patients achieving CR2 before allo-HSCT (CR2 vs. CR1, $p < 0.001$, HR = 4.928, 95%CI: 2.399–10.122) and patients who did not achieve CR (NR vs. CR1, $p = 0.001$, HR = 2.720, 95%CI: 1.522–4.860) (Table 4, Fig. 2F). Other independent adverse risk factor for LFS was mutated BCORL1 (yes *vs.* no, $p < 0.001$, HR = 6.374, 95%CI: 2.280-17.821).

Table 4
Univariate and multivariate analysis of patients undergoing allo-HSCT.

	Univariate analysis			Multivariate analysis		
	p-value	HR	95% *CI*	*p*-value	HR	95% *CI*
OS						
WBC						
≥10×10^9/L vs. <10×10^9/L	0.034	0.600	0.375–0.961			
Disease status before allo-HSCT	0.030			0.038		
CR2 vs. CR1	0.200	1.823	0.727–4.569	0.166	1.919	0.763–4.824
NR vs. CR1	0.014	2.258	1.180–4.320	0.021	2.168	1.123–4.188
Mutated BCORL1	0.096	2.679	0.839–8.553			
Mutated KRAS	0.019	4.024	1.257–12.885	0.016	4.230	1.306–13.694
EMM (+) vs. EMM (-)	0.470	1.192	0.740–1.920			
LFS						
Extramedullary infiltration	0.059	2.108	0.971–4.578			
Disease status before allo-HSCT	< 0.001			< 0.001		
CR2 vs. CR1	< 0.001	4.505	2.206-9.200	< 0.001	4.928	2.399–10.122
NR vs. CR1	0.001	2.630	1.477–4.682	0.001	2.720	1.522–4.860
Mutated BCORL1	0.002	4.892	1.772–13.508	< 0.001	6.374	2.280-17.821
Mutated SETBP1	0.012	3.654	1.334–10.007			
EMM (+) vs. EMM (-)	0.323	1.235	0.813–1.876			

NCCN, National Comprehensive Cancer Network; Allo-HSCT, allogeneic hematopoietic stem cell transplantation. CRR, complete remission rate; ORR, overall remission rate.

Discussion

Our study aimed to evaluate the prognostic value of EMM and the effective therapeutic method for these patients. We found that EMM was an inferior prognostic factor in the univariate analysis of all patients.

Multivariate analysis was used to further analyze the independent prognostic value of EMM in OS and LFS. Our study showed that EMM-positive patients tended to have inferior OS compared with EMM-negative patients and EMM was a poor risk factor for LFS in all patients. In other studies, DNMT3A mutations were reported to be associated with decreased OS [8, 17]. Patients with TET2 mutations appeared to have an adverse prognosis in intermediate-risk AML [9]. ASXL1 mutations were related to poor prognosis in AML patients [18, 19]. IDH1 mutations were connected with adverse prognosis in cytogenetically normal acute myeloid leukemia, whereas the prognosis value of IDH2 mutations was controversial [10, 20]. Other epigenomic modifier gene mutations, including EZH2 [21], KMT2C [22], SETD2 [23], and KDM6A [24, 25], were also reported to be associated with leukemia pathogenesis. Our study showed a similar result by analyzing a mixture of these prognostic mutated genes.

Multivariate analysis in EMM-positive patients showed that patients receiving the DCAG regimen had a similar OS and LFS rate as those receiving the “3 + 7” regimen, whereas allo-HSCT could improve the OS and LFS of these patients. Results in our study showed that there were no differences in OS and LFS between the DCAG regimen group and the “3 + 7” regimen group in EMM-positive patients, which was consistent with a previous study of elderly patients treated with induction therapy containing hypomethylating agents [26]. Nonetheless, allo-HSCT was a favorable risk factor in patients who were EMM-positive. Univariate analysis in patients undergoing allo-HSCT revealed that EMM was no longer a poor prognostic factor in patients undergoing allo-HSCT. These results indicated that allo-HSCT might reverse the poor prognosis of these patients, which was in line with previous studies [13, 14, 27]. Our study also showed that EMM-positive patients receiving the DCAG regimen followed by allo-HSCT had a similar long-term survival compared with those receiving the “3 + 7” regimen followed by allo-HSCT. All these results indicated that allo-HSCT might improve the OS and LFS of EMM-positive patients regardless of the types of induction regimen. Our findings also raised the question of whether epigenetic modifier gene mutations need to be taken into account in addition to high-risk patients when selecting transplant patients. More prospective studies are needed to explore this question.

This study also has some limitations. As a singer-center retrospective study, there may be bias in patients, and the results may also be biased. Multicenter prospective studies are still needed to verify these results.

Conclusions

In conclusion, EMM tended to be a poor risk factor for OS and was a poor risk factor for LFS in our cohort. Allo-HSCT might improve the OS and LFS of EMM-positive patients regardless of the types of induction regimen.

Declarations

Competing interest

None.

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Author Contribution

Gao Cj and Dou LP designed the study. Fang S, Huang S, Wang MZ, Wen YN, Wang H, Jiao YF and Wei Y Participated in data collection. Qian K, Gu ZY and Yang JJ performed statistical analysis and data interpretation. Fang S, Huang S and Wang MZ finished manuscript preparation and literature search. Gao Cj and Dou LP provided funds Collection.

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Figures

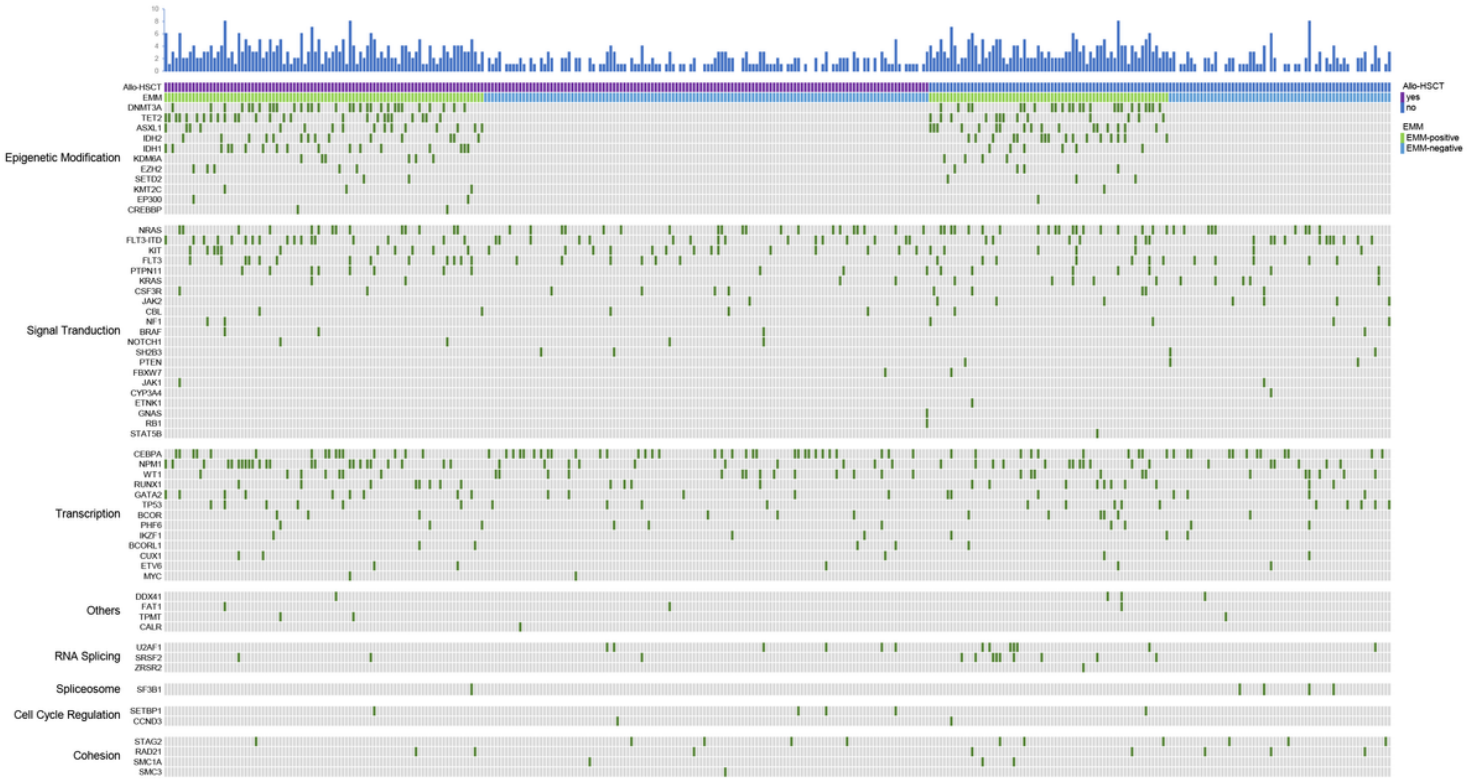

Figure 1

The genomic landscape of 353 AML patients. Mutations were divided into eight functional types, epigenetic modification, signal transduction, transcription, RNA splicing, spliceosome, cell cycle regulation, cohesion, and others.

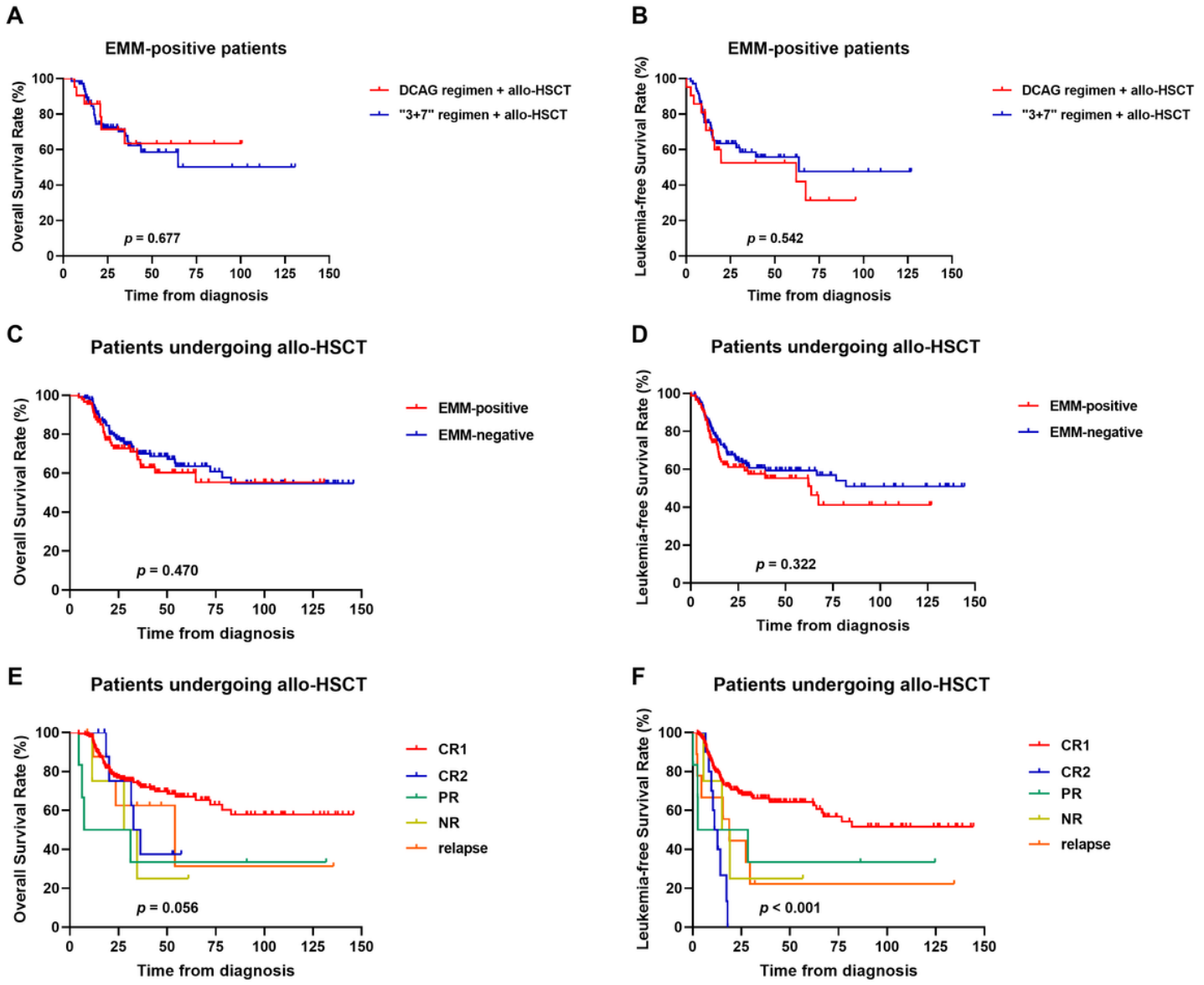

Figure 2

Survival analysis of patients. (A) OS in patients who were EMM-positive; (B) LFS in patients who were EMM-positive; (C) OS between EMM-positive and EMM-negative patients undergoing allo-HSCT; (D) LFS between EMM-positive and EMM-negative patients undergoing allo-HSCT; (E) OS among patients achieving CR1, CR2, PR, NR and relapse before transplantation in patients undergoing allo-HSCT; (F) LFS among patients achieving CR1, CR2, PR, NR and relapse before transplantation in patients undergoing allo-HSCT. OS, overall survival; LFS, leukemia-free survival; EMM, epigenetic modifier gene mutation; allo-HSCT, allogeneic stem cell transplantation; CR1, first complete remission; CR2, second complete remission; PR, partial remission; NR, non-remission.

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