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ORIGINAL RESEARCH

Clinical and biological implications of *IDH1/2* in acute myeloid leukemia with *DNMT3A*^{mut}

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Purpose: The incidence of *DNMT3A* mutations in acute myeloid leukemia (AML) is quite high and often confers a poorer prognosis. Another common gene involved in AML is *IDH1/2*. However, the influence of *IDH1/2* mutations on outcomes in *DNMT3A*-mutated patients remains unknown. This study aims to determine the effect of *IDH1/2*^{mut} on the prognosis in patients with *DNMT3A*-mutated AML.

Patients and methods: We screened patients from The Cancer Genome Atlas database and selected 51 patients with AML and the *DNMT3A* mutation, among which 16 patients (31.4%) had both *DNMT3A* and *IDH1/2*^{mut}.

Results: Among our sample, 11 cases had the *IDH1* mutation (21.7%), and 5 cases had the *IDH2* mutation (9.8%). Patients in the *DNMT3A*^{mut}*IDH1/2*^{wild} group showed a greater number of *NPM1* mutation (P=0.022), and higher event-free survival (EFS) and overall survival (OS) after hematopoietic stem cell transplantation (HSCT) (P=0.010 and P=0.007, respectively). Patients in the *DNMT3A*^{mut}*IDH1/2*^{mut} group showed no increase in EFS or OS after HSCT or chemotherapy. Other factors, like white blood cells, bone marrow blasts, peripheral blood blasts, and mutated recurrent gene numbers had no significant influence on EFS and OS.

Conclusion: The *IDH1/2* gene had little influence on the prognosis of patients with the *DNMT3A* mutation. For patients in the *DNMT3A*^{mut}*IDH1/2*^{wild} group, HSCT had a more favorable therapeutic effect. For patients with *DNMT3A* and *IDH1/2*^{mut}, chemotherapy and HSCT appeared to have similar efficacy.

Keywords: acute myeloid leukemia, molecular mutations, prognosis, next-generation sequencing

Introduction

Acute myeloid leukemia (AML) is an aggressive hematological disease that is characterized by the overproduction of early myeloid precursor cells, often to the exclusion of other cell lines. It leads to anemia, thrombocytopenia, and neutropenia,[1,2] all of which typically have poor outcomes. Recently, some significant improvements have been achieved in our understanding of AML biology and genetics. These fundamental discoveries are now being translated into new diagnostic and therapeutic strategies for this disease.[3]

One of the commonly mutated genes in AML is *DNMT3A*. It encodes a DNA methyltransferase that is localized in the cytoplasm and nucleus, and plays a role in de novo methylation. The prevalence of mutations in *DNMT3A* ranges from 18% to 36% in AML.[4,5] Hajkova et al found significantly lower levels of global DNA

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methylation in AML patients with *DNMT3A* mutations, and this hypomethylation correlated with higher relapse rates and poorer overall survival (OS).[6] Many recent studies have also suggested that the *DNMT3A* mutation should be considered a poor prognostic factor in AML.[5–9] The frequencies of *IDH1* and *IDH2* mutations in AML are approximately 6–16% and 8–19%, respectively.[10,11] IDH is an essential metabolic enzyme that catalyzes the oxidative decarboxylation of isocitrate to α-KG. The *IDH1/2* gene mutations give rise to reduced levels of α-KG and increased levels of 2HG.[10,12] In AML, increasing cellular 2HG levels will inhibit α-KG-dependent enzymes that are important for the demethylation of DNA.[10,13,14] Studies have shown that *IDH1/2*^{mut} display global DNA hypermethylation, and in hematopoietic stem cells, expression of mutant *IDH1/2* increases the expression of stem cell markers and impaired myeloid differentiation.[15] A recent meta-analysis indicated that *IDH1* mutations confer a poorer OS and event-free survival (EFS). However, for *IDH2*, some differences were noted. The *IDH2*^{R140} mutations were associated with better OS among younger cases, whereas outcome was poor for patients with the *IDH2*^{R172} mutation.[10,16]

Mutations in *DNMT3A* and *IDH1/2* have a significant effect on the prognosis of AML patients. They are both involved in the epigenetic regulation of transcription, particularly, alterations in DNA methylation. In addition, these genes both show a high co-mutation rate. However, whether the pattern of association between *DNMT3A*^{mut} and *IDH1/2*^{mut} suggests an interplay in the prognosis of AML remains unknown. This study aims to determine whether *IDH1/2* influences the outcomes of AML patients with the *DNMT3A* mutation, and its effects.

Patients and methods

Patients

Fifty-one patients diagnosed with AML and the *DNMT3A* mutation were enrolled in the study. Experimental data were derived from The Cancer Genome Atlas database (https://cancergenome.nih.gov/). Data on demographic and molecular characteristics of patients with AML, EFS, OS, etc. were also collected and analyzed. Recurrent genetic mutations were detected by next-generation sequencing. Patients were treated in accordance with national comprehensive cancer network guidelines (https://www.nccn.org), with an emphasis on enrollment in therapeutic clinical trials wherever possible. Patients with poor risk received allogeneic hematopoietic stem cell transplantation (allo-HSCT) if they were medically fit for the associated risks of transplantation, and if a suitably matched donor was available. Many patients with intermediate risk also underwent allo-HSCT at some point during the course of the disease.[17] Four patients with intermediate risk received autogenic hematopoietic stem cell transplantation (auto-HSCT). Nineteen patients received allo-HSCT, among which 9 received sibling allo-HSCT (2 high-risk patients and 7 intermediate-risk patients), 6 received matched unrelated donor (MUD) HSCT (1 high-risk patient and 5 intermediate-risk patients), 3 received auto- and MUD HSCT (1 high-risk patient and 2 intermediate-risk patients), and 1 intermediate-risk patient received auto- and sibling allo-HSCT.

To further support the analysis, we used the data of patients in the Clinseq cohort.[18] There were 63 patients with the *DNMT3A* mutation in the Clinseq cohort who were diagnosed between February 1997 and August 2014. Bone marrow or peripheral blood samples were obtained at the time of diagnosis. These patients were treated with intensive induction regimens, including anthracyclines and cytosine arabinoside, according to national guidelines.[19]

Statistical analysis

The primary study endpoints were EFS and OS. The EFS was defined as that time from the date of diagnosis to removal from the study, owing to the absence of complete remission, relapse, or death. The OS was defined as that time from the date of diagnosis to death by any cause. For patients in the Clinseq cohort, we considered OS as the primary outcome.

The demographics and characteristics of the subjects were summarized using descriptive statistics. Intergroup difference was performed using the Student's *t*-test and chi-square test. Survival analyses were performed using the Kaplan–Meier method. A two-sided *P*-value <0.05 was considered statistically significant. All statistical analyses were performed with the SPSS software 20.0 (IBM Corporation, Armonk, NY, USA).

Results

Demographic and biological characteristics

The mutation rates of *IDH* are shown in Figure 1. Sixteen patients had either the *IDH1* or *IDH2* mutation, accounting for 31.4%. The *IDH1* mutations were observed more frequently than *IDH2* mutations. Eleven patients with the *IDH1* mutation had a mutation at R132. Three patients with the *IDH2*-mutation had an *IDH2*^{R140} mutation, and the other 2 had an *IDH2*^{R172} mutation.

The demographic and biological characteristics and the intergroup differences are summarized in Table 1. The

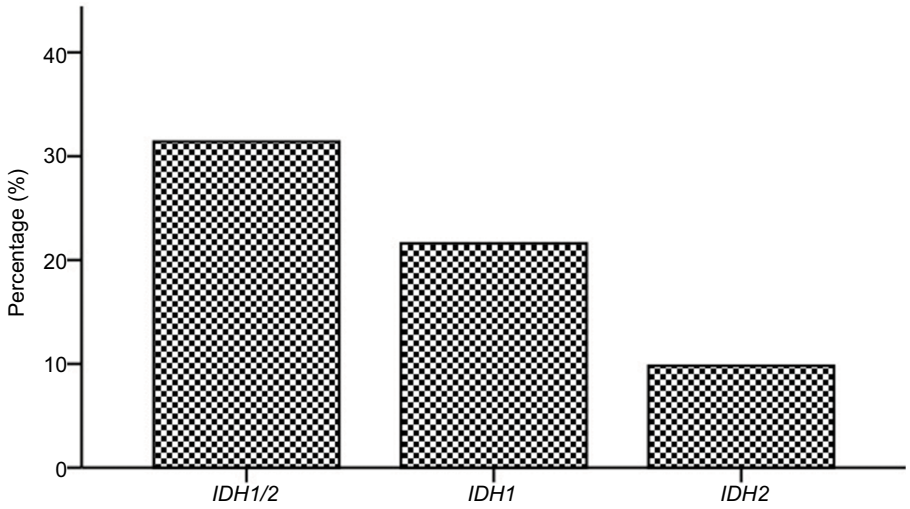

Figure 1 Mutation rate of *IDH*.
Note: Total mutation frequency of *IDH1/2* was 31.4% (16 cases); 21.6% (11 cases) for *IDH1* and 9.8% (5 cases) for *IDH2*.

median age among all 51 patients was 58 years (range: 21–81 years); 27 patients (52.9%) were younger than 60 years. The subjects included 24 males (47.1%) and 27 females (52.9%). In AML FAB, patients with a subtype of M1, 9 (17.6%) of them had *DNMT3A* and *IDH1/2* double mutations while only 4 (7.8%) had only $DNMT3A^{mut}$ (P=0.001). The median white blood cell (WBC) count was 45×10^9/L (range: 1.2×10^9/L–298.4×10^9/L), and 19 cases (37.3%) had counts ≥ 50×10^9/L WBC. The median percentages of bone marrow (BM) blasts and peripheral blood (PB) blasts were 76% (range: 32–100%) and 36% (range, 0–97%), respectively. The percentages of BM blasts and PB blasts in 30 cases (58.8%) and 15 cases (30.0%), respectively, were ≥ 70%. Twenty-eight patients (54.9%) relapsed after receiving treatment. However, these characteristics showed no significant differences between the $DNMT3A^{mut}IDH1/2^{wild}$ and $DNMT3A^{mut}IDH1/2^{mut}$ groups.

The mutation status of the genes under investigation is summarized in Table 1. All genes were associated with AML and had a mutation rate > 5% in our cohort. The most frequently mutated gene was *NPM1*, with 28 mutated cases (54.9%), most of which were concentrated in the $DNMT3A^{mut}IDH1/2^{wild}$ group (P=0.022). Other mutations, including those of *FLT3*-ITD/TKD, *TET2*, *SMC3*, *NRAS*, *KRAS*, *CEBPA*, *PTPN11*, *U2AF1*, *SMC1A*, and *RAD21*, showed no significant intergroup differences (P> 0.05). Among the 51 cases, 23 patients (45.1%) underwent HSCT. In the $DNMT3A^{mut}IDH1/2^{mut}$ group, 11 cases accepted HSCT, whereas 5 did not. The proportion of HSCT acceptance was significantly higher in patients with double mutations (P=0.022).

Comparison of EFS and OS between the $DNMT3A^{mut}IDH1/2^{wild}$ and $DNMT3A^{mut}IDH1/2^{mut}$ groups

In order to determine which patients were more likely to be affected by the *IDH1/2* mutation, we stratified the data by several aspects, such as age, WBC count, percentages of BM blasts and PB blasts, mutated recurrent gene numbers, and frequently mutated genes, such as *FLT3* and *NPM1*. The results of the Kaplan–Meier analysis for EFS and OS are summarized in Table 2. Although the median survival time seemed longer in the double mutation group in several aspects, such as age <60 years, BM blasts or PB blasts <70%, *FLT3* mutation absent, and *NPM1* mutation present, no significant differences were observed among any of these characteristics (P> 0.05).

In the entire cohort, no significant differences were observed in EFS or OS of patients between the $DNMT3A^{mut}IDH1/2^{wild}$ and $DNMT3A^{mut}IDH1/2^{mut}$ groups (Figure 2A and B, P> 0.05). We divided the patients into 2 groups according to treatment, and observed no significant differences in either group (Figure 2C–F, P> 0.05). The HSCT showed better efficacy than chemotherapy in the $DNMT3A^{mut}IDH1/2^{wild}$ group, and led to a higher EFS and OS (Figure 3A and B, P=0.010 for EFS and P=0.007 for OS). However, in the $DNMT3A^{mut}IDH1/2^{mut}$ group, no significant differences were observed between the two treatment methods (Figure 3C and D, P> 0.05).

Considering the differences in effect of *IDH1* and *IDH2* mutations on the prognosis of patients, we divided the entire cohort into 3 groups, more specifically the

Table 1 Clinical and molecular characteristics of patients

Characteristics	Median (range) or n/%			Intergroup difference	
	Total	*DNMT3A*^{mut}*IDH1/2*^{wild}	*DNMT3A*^{mut}*IDH1/2*^{mut}	T/χ^2	*P*-value
Age (years)	58 (21–81)	59 (21–81)	57.5 (42–69)	0.528^	0.600
<60	27/52.9	18/35.3	9/17.6		
≥ 60	24/47.1	17/33.3	7/13.7		
Gender				0.102§	0.749
Male	24/47.1	17/33.3	7/13.7		
Female	27/52.9	18/35.3	9/17.6		
AML FAB subtypes					
M0	3/5.9	1/2.0	2/3.9	1.844§	0.229
M1	13/25.5	4/7.8	9/17.6	11.615§	0.001
M2	11/21.6	9/17.9	2/3.9	1.133§	0.466
M4	12/23.5	10/19.6	2/3.9	1.576§	0.296
M5	11/21.6	10/19.6	1/2.0	3.234§	0.140
M7	1/1.9	1/2.0	0	0.466§	1.000
WBC count/×10^9/L	45 (1.2–298.4)	45.3 (1.4–298.4)	15.2 (1.2–171.9)	1.515^	0.136
<50	32/62.7	19/37.3	13/25.5		
≥ 50	19/37.3	16/31.4	3/5.9		
BM blasts/%	76 (32–100)	74 (32–100)	81.5 (42–99)	1.427^	0.160
<70	21/41.2	17/33.3	4/7.8		
≥ 70	30/58.8	18/35.3	12/23.5		
PB blasts/%	36 (0–97)	16.5 (0–96)	51.5 (6–97)	1.859^	0.069
<70	35/70.0	25/50.0	10/20.0		
≥ 70	15/30.0	9/18.0	6/12.0		
Relapse				0.017§	1.000
Yes	28/54.9	19/37.3	9/18.0		
No	23/45.1	16/31.4	7/13.7		
Mutated recurrent genes	6 (2–11)			1.670^	0.102
<5	15/29.4	15/29.4	0		
≥ 5	36/70.6	20/39.2	16/31.4		
NPM1				5.268§	0.022
W288	26/51.0	22/43.1	4/7.8		
Others	2/3.9	1/2.0	1/2.0		
Wild type	23/45.1	12/23.5	11/21.6		
FLT3				2.519§	0.112
FLT3-ITD	12/23.5	11/21.6	1/2.0		
FLT3-TKD	9/17.6	6/11.8	3/5.9		
Wild type	30/58.8	18/35.3	12/23.5		
TET2				0.012§	1.000
Mutation	6/11.8	4/7.8	2/3.9		
Wild type	45/88.2	31/60.8	14/27.5		
SMC3				3.109§	0.159
Mutation	6/11.8	6/11.8	0		
Wild type	45/88.2	29/56.9	16/31.4		
NRAS				0.333§	1.000
Mutation	5/9.8	4/7.8	1/2.0		
Wild type	46/90.2	31/60.8	15/29.4		
KRAS				0.700§	0.581
Mutation	4/7.8	2/3.9	2/3.9		
Wild type	47/92.2	33/64.7	14/27.5		
CEBPA					
Single mutation	2/3.9	1/2.0	1/2.0	0.335§	0.533
Double mutation	1/2.0	1/2.0	0	0.466§	1.000
Wild type	48/94.1	33/64.7	15/29.4		
PTPN11				1.844§	0.229
Mutation	3/5.9	1/2.0	2/3.9		
Wild type	48/94.1	34/66.7	14/27.5		

(*Continued*)

Table 1 (*Continued*)

Characteristics	Median (range) or n/%			Intergroup difference	
	Total	*DNMT3A*^{mut}*IDH1/2*^{wild}	*DNMT3A*^{mut}*IDH1/2*^{mut}	T/χ^2	*P*-value
U2AF1				1.457§	0.543
Mutation	3/5.9	3/5.9	0		
Wild type	48/94.1	32/62.7	16/31.4		
SMC1A				0.006§	1.000
Mutation	3/5.9	2/3.9	1/2.0		
Wild type	48/94.1	33/64.7	15/29.4		
RAD21				1.457§	0.543
Mutation	3/5.9	3/5.9	0		
Wild type	48/94.1	32/62.7	16/31.4		
MLL-PTD				0.006§	1.000
Presence	3/5.9	2/3.9	1/2.0		
Absence	48/94.1	33/64.7	15/29.4		
HSCT				5.268§	0.022
Yes	23/45.1	12/23.5	11/21.6		
Allo-HSCT	19/37.3	9/17.6	10/19.6		
Auto-HSCT	4/7.8	3/5.9	1/2.0		
None	28/54.9	23/45.1	5/9.8		

Notes: ^Student's *t*-test; §chi-square test.

Abbreviations: AML FAB, the French-American-British classification of acute myeloid leukemia; WBC, white blood cell; BM, bone marrow; PB, peripheral blood; ITD, internal tandem duplication; TKD, tyrosine kinase domain; HSCT, hematopoietic stem cell transplantation; Allo-HSCT, allogeneic-hematopoietic stem cell transplantation; Auto-HSCT, autogenic-hematopoietic stem cell transplantation; mut, mutation; wild, wild type.

Table 2 Comparison of EFS and OS between *DNMT3A*^{mut}*IDH1/2*^{wild} and *DNMT3A*^{mut}*IDH1/2*^{mut} groups

Prognostic factor	EFS				OS			
	DNMT3A^{mut} *IDH1/2*^{wild}	*DNMT3A*^{mut} *IDH1/2*^{mut}	χ^2	*P*-value	*DNMT3A*^{mut} *IDH1/2*^{wild}	*DNMT3A*^{mut} *IDH1/2*^{mut}	χ^2	*P*-value
Age								
<60 years	8.5	14.9	0.225	0.635	16.3	24.8	0.186	0.667
≥ 60 years	6.9	4.9	0.619	0.431	8.1	7.8	2.228	0.136
WBC								
<50×10^9/L	8.4	13.8	0.732	0.392	10.2	21.5	0.795	0.373
≥ 50×10^9/L	8.1	17.2	1.108	0.293	10.2	27.1	0.647	0.421
BM blasts								
<70%	8.4	14.9	1.432	0.231	10.2	28.4	1.601	0.206
≥ 70%	6.4	5.2	0.490	0.484	7.5	12.0	1.055	0.304
PB blasts								
<70%	8.1	13.8	0.622	0.430	9.9	21.5	1.815	0.178
≥ 70%	7.5	2.7	0.212	0.645	7.5	6.6	0.243	0.622
Mutated recurrent genes								
≥ 5	8.2	8.7	1.238	0.266	9.9	20.1	2.570	0.109
NPM1								
Mutated	6.9	13.8	2.084	0.149	7.5	24.8	2.623	0.105
Wild type	8.5	8.6	<0.001	0.998	14.6	20.1	0.001	0.972
FLT3-ITD/TKD								
Present	6.9	2.7	0.066	0.798	7.9	6.6	0.012	0.913
Absent	8.4	13.8	0.980	0.322	10.2	21.5	1.129	0.288
HSCT								
Yes	9.9	14.9	0.003	0.960	16.4	24.8	0.010	0.921
None	5.9	5.2	0.287	0.592	7.7	5.2	0.116	0.734

Abbreviations: EFS, event-free survival; OS, overall survival; WBC, white blood cell; BM, bone marrow; PB, peripheral blood; ITD/TKD, internal tandem duplication and tyrosine kinase domain; HSCT, hematopoietic stem cell transplantation; mut, mutation; wild, wild type.

IDH1/2^{wild}, *IDH1* mutation and *IDH2* mutation groups. We did not separate *IDH2*^{R140} and *IDH2*^{R172} mutations because of the small sample size. The results of Kaplan–Meier analysis for EFS and OS are shown in Figure 4A–D (P> 0.05). No significant differences were observed among the 3 groups.

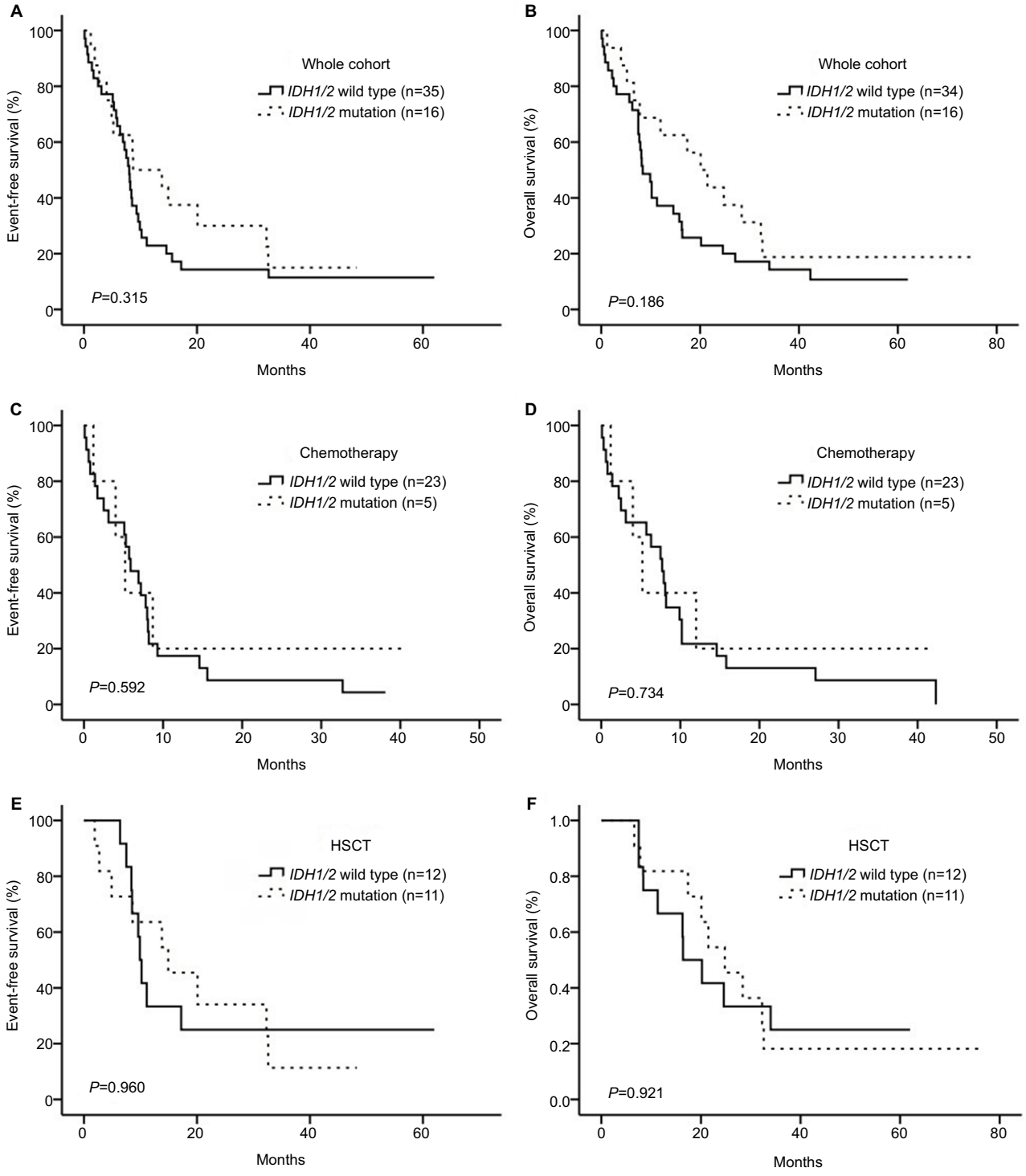

Figure 2 Kaplan–Meier analysis of EFS and OS.
Notes: (**A**,**B**) *IDH1*/2 mutation status had no effect on EFS or OS in the whole cohort. (**C**,**D**) *IDH1*/2 mutation status had no effect on EFS or OS for the patients subjected to chemotherapy. (**E**,**F**) *IDH1*/2 mutation status had no effect on EFS or OS for the patients subjected to HSCT.
Abbreviations: EFS, event-free survival; OS, overall survival; HSCT, hematopoietic stem cell transplantation.

We further verified our results in the Clinseq cohort. When patients with mutations of *IDH1* or *IDH2* were grouped together, the results of Kaplan–Meier analysis for OS showed no significant differences between the $DNMT3A^{mut}IDH1/2^{wild}$ and $DNMT3A^{mut}IDH1/2^{mut}$ groups (Figure 5A, P=0.128). In Figure 5B, patients with the $IDH2^{R140}$ mutation were considered a single group. Furthermore, because of their relatively consistent effects on the prognosis, patients with mutations

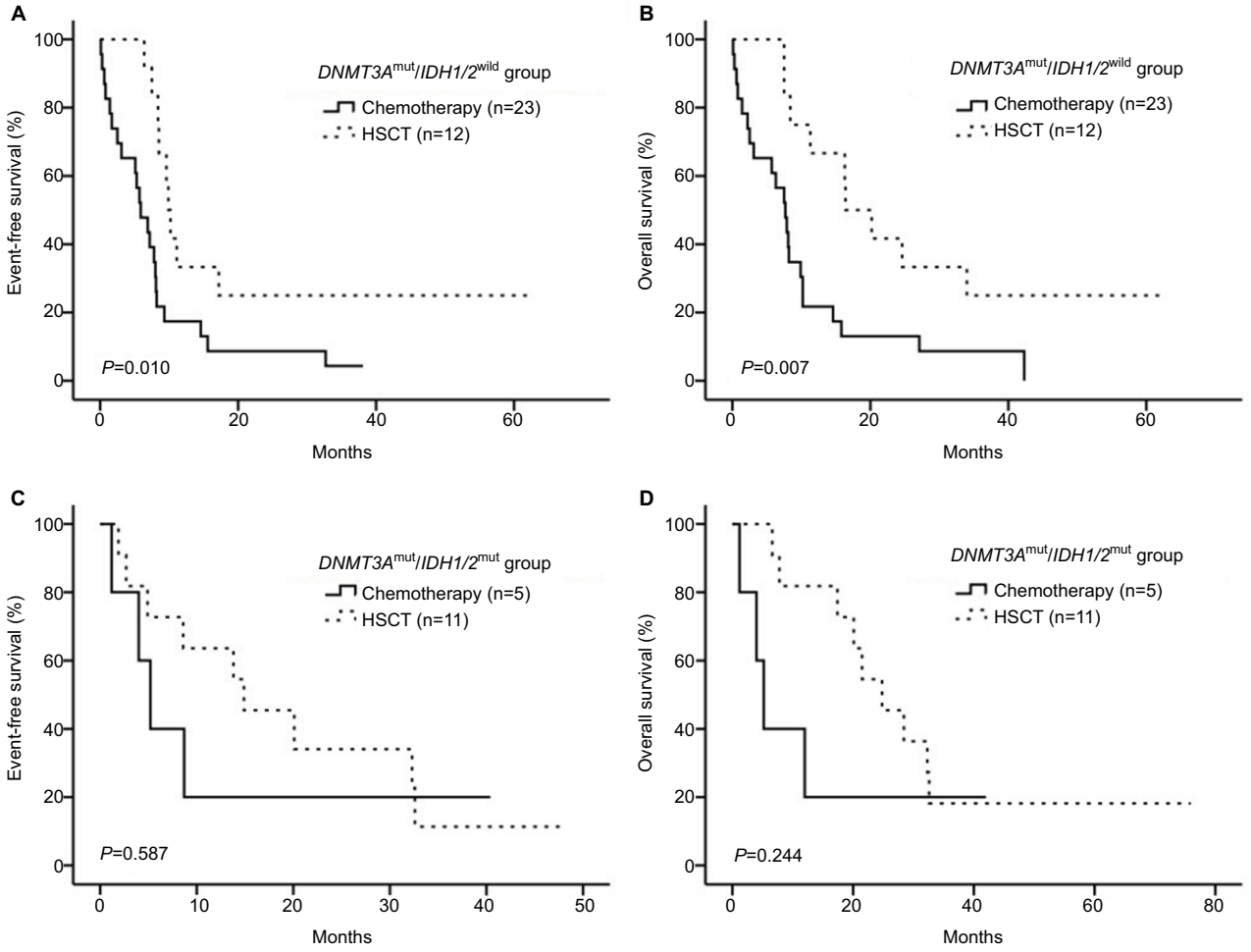

Figure 3 Patient responses to treatment.
Notes: (**A**,**B**) HSCT had a better therapeutic effect for patients with the *DNMT3A*^{mut} and *IDH1/2*^{wild}. (**C**,**D**) For the patients with both *DNMT3A* and *IDH1/2*^{mut}, HSCT and chemotherapy were considered to have similar efficacy.
Abbreviations: HSCT, hematopoietic stem cell transplantation; mut, mutation; wild, wild type.

of *IDH1* and *IDH2*^{R172} were divided into 2 groups. No significant differences were observed in the OS among these 3 groups (*P=0.124*).

Discussion

We synthetically analyzed different aspects of the effects of *IDH1/2*^{mut} on the outcomes of patients with *DNMT3A*-mutated AML; however, no significant differences were found. The HSCT could be a more favorable option for patients with the *DNMT3A* mutation. However, HSCT and chemotherapy showed no significant differences in patients with double mutations. The *DNMT3A*^{mut}*IDH1/2*^{mut} group showed relatively lower rates of *NPM1* mutation.

Previous studies have indicated that *NPM1* and double-mutated *CEBPA* have positive effects, whereas *FLT3*-ITD, *TET2*, *KRAS*, *PTPN11*, *U2AF1*, and *MLL*-PTD mutations have adverse effects on the outcomes of AML patients.[20–27] Mutations of *SMC3*, *RAD21*, and *NRAS* were thought to have little to no influence on those studies, whereas the effects of other gene mutations, such as that of *SMC1A*, on the prognosis of AML had not been clearly determined.[20–27]

In our cohort, 54.9% of the patients had *NPM1* mutations. Patients in the *DNMT3A*^{mut}*IDH1/2*^{mut} group had a lower mutation rate of *NPM1* (45.1% versus 9.8%). In another study, about 80% of *DNMT3A*-mutated patients had *NPM1* mutations, and 65.4% of the double-mutation patients concurrently harbored *NPM1* mutations.[8] Rakheja et al indicated that *IDH1*^{R132} and *IDH2*^{R140} mutations are frequently accompanied by *NPM1* mutations in AML.[10] In our cohort, 87.5% of the patients harbored *IDH1*^{R132} or *IDH2*^{R140}; however, we observed no correlation between *NPM1* and *IDH1/2*. The reason for this difference might be due to the age distribution of the sample, the small sample size, or the research background of our cohort.

Many studies have attempted to elucidate the effects of multiple gene mutations on the outcomes of AML. More

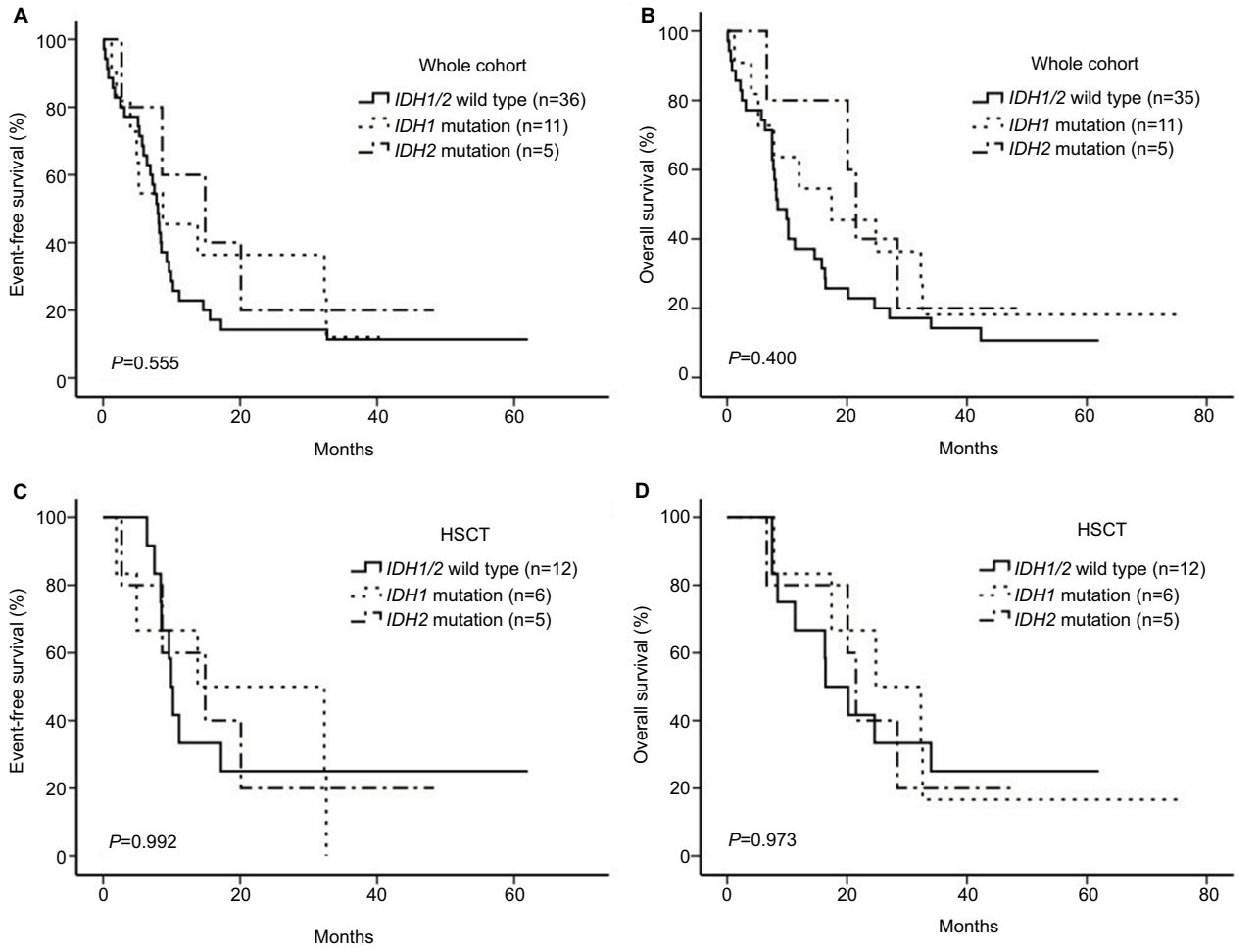

Figure 4 Patient responses to treatment.
Notes: (**A**,**B**) *IDH1* and *IDH2* mutation status had no effect on EFS or OS in the whole cohort. (**C**,**D**) *IDH1* and *IDH2* mutation status had no effect on EFS or OS for patients subjected to HSCT.
Abbreviations: EFS, event-free survival; OS, overall survival; HSCT, hematopoietic stem cell transplantation.

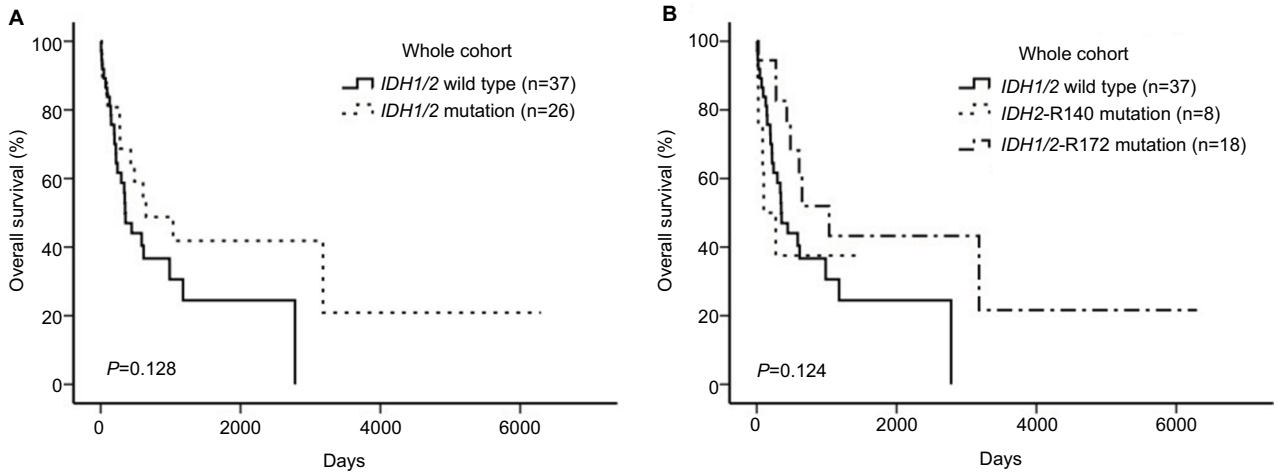

Figure 5 Kaplan–Meier analysis of OS of patients from the Clinseq cohort.
Notes: (**A**) *IDH1*/2 mutation status had no effect on OS in the whole cohort. (**B**) Different mutations of *IDH* had no effect on OS for patients in the whole cohort.
Abbreviation: OS, overall survival.

specifically, studies have shown that *FLT3*-ITD with the *DNMT3A*^{R882} double mutation is a poor prognostic factor in AML;[28] whereas *NPM1* mutations do not seem to have a significant effect on the outcomes of patients with *DNMT3A*-mutated AML.[8] Alternatively, *IDH1/2*^{mut} constitute a poor prognostic factor in *NPM1*-mutated cytogenetically normal-AML (CN-AML) without *FLT3-ITD*.[29] Our study revealed that *IDH1/2*^{mut} have little influence on the outcomes of patients with *DNMT3A*-mutated AML.

The HSCT has been confirmed as an effective therapy for intermediate- or high-risk patients with AML. Patients at higher risk usually benefit more from transplant therapy. The survival of CN-AML patients with *DNMT3A*^{mut} could be improved following allo-HSCT.[30] Nevertheless, as we have mentioned before, the *FLT3*-ITD and *DNMT3A*^{R882} double mutation is a poor prognostic factor in AML. Patients with this condition have significantly lower 2-year OS and leukemia-free survival (the duration from post-transplantation to recurrence of leukemia or death) following allo-HSCT, than patients with single *FLT3*-ITD or *DNMT3A*^{mut}.[28]

In comparison with chemotherapy, our results demonstrate that HSCT had a more favorable therapeutic effect on patients with the *DNMT3A* mutation. When *IDH1/2*^{mut} were taken into account however, the effects of these two therapies were statistically equivalent. Patients with the *DNMT3A* and *IDH1/2* double mutation showed no gain in EFS or OS after either HSCT or chemotherapy. This result suggests that *IDH1/2*^{mut} might not be a strong biomarker for HSCT therapy in patients with the *DNMT3A* mutation. Analysis of data from the Clinseq cohort further supported the view that *IDH1/2*^{mut} in patients with AML who received chemotherapy had little effect on the outcomes of those with the *DNMT3A* mutation. The results of the analysis in which different mutations of *IDH* were separated also showed that they had no impact on the prognosis of these patients, even though mutations of *IDH1*, *IDH2*^{R140}, and *IDH2*^{R172} might have different effects on the outcome.

In addition to HSCT, targeted therapy is now one of the more popular treatment choices that can show good efficacy. Enasidenib (AG-221) is a reversible and selective inhibitor of mutant *IDH2*.[3,31,32] Inhibitors of *IDH1*, such as AG-120 and IDH305, are also under investigation.[3] Although our study showed that *IDH1/2*^{mut} have no influence on the outcomes of AML patients with *DNMT3A*^{mut}, because of the development of novel, effective target drugs, *IDH1/2* inhibitors might have positive effects on the overall prognosis of patients with double mutations.

Limitations

Several limitations of the present study need to be acknowledged. Our study is a retrospective study with a relatively small sample size, and some bias needs to be considered. In some groups, the number of samples was less than 5, thus limiting further statistical analysis. Therefore, the present results need to be verified in larger cohorts.

Conclusion

We propose that *IDH1/2* has no impact on the prognosis of AML patients with the *DNMT3A* mutation. Furthermore, HSCT showed a more favorable therapeutic effect for patients with the *DNMT3A*, but without the *IDH1/2* mutation. For patients with double mutations, the efficacy of HSCT was similar to that of chemotherapy.

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Author contributions

Xiaoyan Ke and Lin Fu designed the study; Xinpei Zhang wrote the manuscript; Xinpei Zhang, Jinlong Shi, Jilei Zhang, Xinrui Yang, Gaoqi Zhang, Siyuan Yang, and Jing Wang performed statistical analyses and analyzed the data. Xiaoyan Ke and Lin Fu coordinated the study over the entire experimental period. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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