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ORIGINAL RESEARCH

High expression of dedicator of cytokinesis 1 adversely influences the prognosis of acute myeloid leukemia patients undergoing allogeneic hematopoietic stem cell transplantation

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Background: Overexpression of dedicator of cytokinesis 1 (*DOCK*1) has been confirmed as an unfavorable prognostic marker in acute myeloid leukemia (AML).

Purpose: This study is to explore the clinical implications of *DOCK1* on AML patients underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Patients and methods: We analyzed 71 de novo AML patients treated with allo-HSCT and divided them into two groups ($DOCK1^{high}$ vs $DOCK1^{low}$) by the median expression level of *DOCK1*.

Results: High *DOCK1* expression was associated with older age (P=0.019), wild-type *CEBPA* (P=0.002), *IDH1/2* mutations (P=0.010) and *RUNX1* mutation (P=0.005). Univariate analyses showed that $DOCK1^{high}$ and *RUNX1* mutation were associated with shorter OS (P<0.001, P=0.024). Multivariate analysis confirmed the negative effect of high *DOCK1* level on overall survival (P=0.010).

Conclusion: Our results demonstrate that in AML patients who received allo-HSCT, high *DOCK1* expression might have a persistent negative prognostic impact post-transplant.

Keywords: acute myeloid leukemia, allo-HSCT, *DOCK1*, prognosis

Background

Acute myeloid leukemia (AML) is a malignant disease of hemopoietic stem cells. It is characterized by clonal expansion of differentiated blasts of myeloid lineage.[1] The current version of the WHO classification provides guidance on AML diagnosis, treatment and prognostication.[2] The outcome of AML patients is heterogeneous, depending on both patient- and disease-related risk factors. Genomic abnormalities account for at least 60% of the variables in AML prognostication.[3] For example, *FLT3-ITD* has a clear correlation with a poor outcome, while mutations in *NPM1* bode a particularly better prognosis.[4] The presence of biallelic mutations of *CEBPA* is an independent factor for favorable outcome in AML patients.[5] A recent meta-analysis indicated that *IDH1* mutations confer a poorer survival,[6] so do genetic aberrations of *TP53*[7] or *RUNX1*.[8] Genetic factors are incorporated to treatment design because they determine disease sensitivity to treatment as well as the tolerability of therapy.

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has a strong anti-leukemic effect and it is a commonly used option for AML post-remission consolidation therapy.[9] It especially improves the outcomes of patients with poor-risk

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or intermediate-risk disease.[10] Although allo-HSCT can decrease the frequency of relapse and prolong survival, many patients still relapse post-transplant.[1] An increasing number of research focusing on post-transplant relapse have pointed out several factors including WBC count at diagnosis,[11] cytogenetic risk status,[12] initial induction response,[13] and most importantly, minimal residual disease (MRD) status at the time of transplantation.[14] In the MRD-negative patients who still experience relapse, genetic alterations might play an even bigger role in leukemogenesis and prognostication.[15]

The dedicator of cytokinesis 1 (DOCK) family is a class of the atypical Rho guanine nucleotide exchange factors (GEFs).[16] As a major Rac GEF, DOCK proteins are involved in various cellular processes, such as cell adhesion, cell migration, actin cytoskeleton, and tumorigenesis.[17,18] Sze-Hwei Lee, et al, have discovered that high expression of *DOCK1* implied poor prognosis in AML patients.[19] However, it is yet to be determined whether the expression level of *DOCK1* has prognostic value in AML patients undergoing allo-HSCT. In this study, we will focus on the prognostic significance of *DOCK1* in a cohort of AML patients undergoing allo-HSCT and discuss its clinical implications.

Patients and methods

Patients

A group of 71 de novo AML patients (41 males, 30 females) from The Cancer Genome Atlas (TCGA) (https://cancergenome.nih.gov/) database, who had undergone allo-HSCT and had available *DOCK1* expression data, were included in the study. TCGA database was originated from a single institution tissue banking protocol that was approved by the Washington University Human Studies Committee. All patients were between ages 18 and 88 and had previously untreated de novo AML. The samples were collected between November of 2001 and March of 2010. Clinical characteristics, as well as risk groups and the frequencies of known recurrently mutated genes, were highly representative of adult patients with de novo AML. The patients were treated in accordance with NCCN guidelines (www.nccn.org), with an emphasis on enrollment in therapeutic clinical trials whenever possible. Those patients with intermediate or unfavorable risk underwent allogeneic stem cell transplant if they were medically fit for transplantation, and if a suitably matched donor was available. Next-generation sequencing was utilized for detecting genetic mutations. Written informed consent was obtained from each patient approved by the Human Research Ethics Committee of Washington University. Clinical and molecular information at diagnosis were collected. All the data was publicly available on the website of the TCGA database.

Statistical analysis

Descriptive statistics were used to summarize demographics, clinical and molecular information. Continuous variables were described in the form of the median with range. The Mann–Whitney *U* test was used for comparing two groups of numeric variables, and chi-square analysis was applied to the comparison of categorical variables. The clinical endpoint of this study was overall survival (OS), which was defined as the time from diagnosis to death or was censored at the last follow-up. The OS rate was calculated using the Kaplan–Meier method, and the survival curves were plotted. The log-rank test was used to analyze significant differences between survival distributions. A cox proportional hazard model was applied to univariable and multivariable analyses to assess possible prognostic factors. The relapse-free survival (RFS) rate, defined as the time from the date of diagnosis to relapse, was also analyzed. The level of statistical significance was set at $P<0.05$ for all analyses. SPSS software version 20.0 and GraphPad Prism software version 6.0 were used for all the statistical analyses.

Results

Association of *DOCK1* expression level with demographic characteristics and prognostic factors

The total of 71 patients was divided into two groups ($DOCK1^{high}$ group and $DOCK1^{low}$ group) based on the median *DOCK1* expression level. High *DOCK1* expressers were associated with older age (≥60, $P=0.019$), with an average age of 55 compared with 51 in $DOCK1^{low}$ group ($P=0.010$). Patients with higher *DOCK1* expression had a lower percentage of peripheral blood (PB) blasts ($P=0.010$) and fewer *IDH1/2* mutations ($P=0.010$). *FLT3-ITD* appeared more frequently in $DOCK1^{high}$ patients ($P=0.051$). All the patients with *CEBPA* double mutation were in $DOCK1^{low}$ group while *RUNX1* mutations were observed only in $DOCK1^{high}$ group ($P=0.005$). There were no differences in other clinical factors including WBC count, FAB subtypes and karyotypes, as well as

molecular prognostic features like *TP53, MLL-PTD* and *NPM1* mutations. As for the ratios of relapse, no differences were found between the two groups. There was no difference between the two groups on the transplant status. The summary of the association between *DOCK1* expression level and the demographic and prognostic factors is displayed in Table 1.

Higher expression level of *DOCK1* indicated shorter OS in AML patients undergoing allo-HSCT

Univariate and multivariate analysis using cox proportional hazard models synthesized possible prognostic elements including *DOCK1* expression level (high vs low), age (≥60 vs <60 years), WBC (≥30 vs <30×10^9/L), risk stratification (poor vs non-poor) and genetic mutation like *FLT3-ITD, NPM1, DNMT3A, CEBPA* double mutation, *IDH1* and *RUNX1*. The results are shown in Tables 2 and 3.

Univariate analysis and Kaplan–Meier survival curve both revealed that patients undergoing allo-HSCT in *DOCK1*^{high} group had a shorter OS (Table 2, Figure 1, both $P<0.001$). Mutations in *RUNX1* also had an adverse effect on OS (Table 2, $P=0.024$). The result of multivariate analysis further demonstrated the unfavorable effect of high *DOCK1* expression (Table 3, $P=0.010$). Multivariate analysis also showed that patients who received a transplant in CR1/2 had longer OS (Table 3, $P=0.043$). *RUNX1, FLT3-ITD* and *NPM1* were not correlated with the OS in AML patients undergoing allo-HSCT in our cohort. The results of univariate and multivariate analysis of RFS, as well as the Kaplan-Meier curve, were provided in Tables S1and S2 and Figure S1 in the Supplementary Appendix.

Discussion

In our study, overexpression of *DOCK1* can shorten OS in AML patients undergoing allo-HSCT, implying that allo-HSCT cannot eliminate the negative effect of *DOCK1* overexpression. As an important prognostic marker, *DOCK1* might be a potential therapeutic target for AML treatment.

Sze-Hwei Lee, et al[19] showed that higher *DOCK1* expression was associated with many other prognostic factors including intermediate-risk cytogenetics. As a curative-intent method, allo-HSCT has a well-documented anti-tumor effect especially on high-risk and intermediate-risk AML patients.[20] The prognostic influence of some prognostic mutations can be ameliorated by allo-HSCT.[21] For example, Ma Y, et al concluded that allo-HSCT could efficiently reduce relapse and boost survival for patients with *FLT3-ITD* mutation.[22] Yang Xu, et al have shown that allo-HSCT could prolong survival in cytogenetically normal AML.[23] Our study came to similar conclusions that allo-HSCT could overcome the adverse effect of some prognostic factors, such as *FLT3-ITD, DNMT3A* and *RUNX1*. However, the inferior outcome associated with *DOCK1* overexpression could not be completely overcome by allo-HSCT. Though transplant status in CR1/2 prolongs survival to some extent, the statistical significance still brings the level of *DOCK1* expression to our attention.

Consistent with the previous study,[19] our study showed that patients with *DOCK1* overexpression were older and had higher PB blast percentage at diagnosis. But there was no distinct relationship between *DOCK1* expression and karyotype or cytogenetics, probably due to the implementation of allo-HSCT. We found a negative correlation between *DOCK1* expression and frequencies of *FLT3-ITD, RUNX1* mutations in our cohort. Since these were well-defined poor prognostic factors, the negative correlation could further imply that high *DOCK1* expression could be an independent risk factor for AML outcome post-transplant.

As a GEF, DOCK1 plays multiple roles in physiological and pathological conditions. Researches have shown that DOCK1 regulates cell motility and tumor invasion in glioma cell by binding with engulfment and cell motility protein 1 (ELMO1).[24,25] Laurin, et al, reported that DOCK1 was a critical regulator in HER2-mediated breast cancer metastasis.[18] In human colorectal cancer, DOCK1 was simulated by cortactin, which could promote cell migration and invasion.[26] Downregulation of DOCK1 may prevent epithelial–mesenchymal transition in bladder cancer.[16] Furthermore, in vivo researches by Tajiri, et al. have demonstrated the effectiveness of targeting DOCK1 in the ras-driven cancer cell.[27] Hence, targeted therapy against DOCK1 deserves attention for future anti-cancer drug design. As demonstrated by the current study, the unfavorable effect of *DOCK1* could not be eliminated by allo-HSCT, it would be worth investigating *DOCK1*-targeted therapy in AML patients for post-transplant maintenance.

Our study is limited by sample size and its retrospective nature. A larger cohort study is in need to confirm our findings. Further bench work exploring the role of DOCK1 in leukemogenesis are also imperative.

Table 1 Clinical and molecular characteristics of *DOCK1*^{high} and *DOCK1*^{low} patients

Characteristics	*DOCK1*^{high} (n=36)	*DOCK1*^{low} (n=35)	*U*/χ^2	*P*-value
Age/years, median (range)	55 (23–72)	51 (18–69)	854.0*	0.010
Age group/n (%)			5.481§	0.019
<60 years	22 (61.1)	30 (85.7)		
≥60 years	14 (38.9)	5 (14.3)		
Gender/n (%)			0.739§	0.390
Male	19 (52.8)	22 (62.9)		
Female	17 (47.2)	13 (37.1)		
WBC count/×10^9/L, median (range)	23.35 (0.6–102.5)	32.4 (1.2–223.8)	506.0*	0.154
BM blasts/%, median (range)	70 (30–100)	71 (34–99)	585.5*	0.609
PB blasts/%, median (range)	41 (0–91)	62.5 (5–96)	393.0*	0.010
FAB subtypes/n (%)			9.396§	0.225
M0	7 (19.4)	2 (5.9)	3.022§	0.151
M1	9 (25.0)	14 (41.2)	1.823§	0.177
M2	7 (19.4)	11 (32.4)	1.347§	0.246
M3	0 (0.0)	1 (2.9)	1.043§	0.493
M4	8 (22.2)	5(14.7)	0.747§	0.387
M5	3 (8.3)	1 (2.9)	1.001§	0.614
M6	1 (2.8)	0 (0.0)	0.986§	1.000
M7	1 (2.8)	0 (0.0)	0.986§	1.000
Karyotype/n (%)			8.636§	0.472
Normal	16 (44.4)	17 (48.6)	0.122§	0.727
Complex	7 (19.4)	4 (11.4)	0.871§	0.351
8 Trisomy	4 (11.1)	2 (5.7)	0.668§	0.674
inv(16)/CBFβ-MYH11	4 (11.1)	1 (2.9)	1.847§	0.357
11q23/MLL	2 (5.6)	1 (2.9)	0.319§	1.000
−7/7q-	1 (2.8)	2(5.7)	0.378§	0.614
t(15;17)/PML-RARA	0 (0.0)	1 (2.9)	1.043§	0.493
t(9;22)/BCR-ABL1	1 (2.8)	1 (2.9)	0.000§	1.000
t(8;21)/RUNX1-RUNX1T1	0 (0.0)	1 (2.9)	1.043§	0.493
Others	1 (2.8)	5 (14.3)	3.038§	0.107
Risk/n (%)			1.574§	0.455
Good	4 (11.1)	3 (8.8)	0.102§	1.000
Intermediate	18 (50.0)	22 (64.7)	1.544§	0.214
Poor	14 (38.9)	9 (26.5)	1.222§	0.269
FLT3-ITD			5.937§	0.015
Presence	13 (36.1)	4 (11.4)		
Absence	23 (63.9)	28 (88.6)		
NPM1			0.378§	0.539
Mutation	8 (22.2)	10 (28.6)		
Wild type	28 (77.8)	25 (71.4)		
CEBPA			9.273§	0.010
Single mutation	0 (0.0)	5 (14.3)		
Double mutation	0 (0.0)	3 (8.6)	3.222§	0.115
Wild type	36 (100.0)	27 (77.1)	9.273§	0.002
DNMT3A			2.124§	0.145
Mutation	6 (16.7)	11 (31.4)		
Wild type	30 (83.3)	24 (68.6)		

(*Continued*)

Table 1 (Continued).

Characteristics	*DOCK1*^{high} (n=36)	*DOCK1*^{low} (n=35)	*U*/χ^2	*P*-value
IDH1/2			6.601§	0.010
Mutation	4 (11.1)	13 (37.1)		
Wild type	32 (88.9)	27 (62.9)		
WT1			2.129§	0.260
Mutation	6 (16.7)	2 (5.7)		
Wild type	30 (83.3)	33 (94.3)		
RUNX1			8.765§	0.005
Mutation	8 (22.2)	0 (0.0)		
Wild type	28 (77.8)	35 (100.0)		
MLL-PTD			1.001§	0.614
Presence	3 (8.3)	1 (2.9)		
Absence	33 (91.7)	34 (97.1)		
NRAS/KRAS			1.522§	0.260
Mutation	2 (5.6)	5 (14.3)		
Wild type	34 (94.4)	30 (85.7)		
TET2			0.001§	1.000
Mutation	2 (5.6)	2 (5.7)		
Wild type	34 (94.4)	33 (94.3)		
TP53			4.121§	0.115
Mutation	4 (11.1)	0(0.0)		
Wild type	32 (88.9)	35 (100.0)		
KIT			3.045§	0.239
Mutation	3 (8.3)	0 (0.0)		
Wild type	33 (91.7)	3 5(100.0)		
PTPN11			2.029§	0.199
Mutation	1 (2.8)	4 (11.4)		
Wild type	35 (97.2)	31 (88.6)		
PHF6			1.001§	0.614
Mutation	3 (8.3)	1 (2.9)		
Wild type	33 (91.7)	34 (97.1)		
Relapse			0.029§	0.864
Yes	24 (66.7)	24 (68.6)		
No	12 (33.3)	11 (31.4)		
HSCT			0.145§	0.930
Haplo	1 (2.8)	1 (2.8)	0.000§	1.000
Sib allo	19 (52.8)	20 (57.1)	0.144§	0.705
MUD	16 (44.4)	14 (40.0)	0.137§	0.712
Transplant status/n (%)			1.735§	0.420
CR1	19 (52.8)	21 (60.0)	0.376§	0.540
CR2	5 (13.9)	7 (20.0)	0.472§	0.492
Others	12 (33.3)	7 (20.0)	1.610§	0.205

Note: *Mann–Whitney *U* test; §chi-square test.

Abbreviations: WBC, white blood cell; BM, bone marrow; PB, peripheral blood; FAB, French American British; HSCT, hematopoietic stem cell transplantation; Haplo, haploidentical; Allo, allogeneic; MUD, matched unrelated donor; CR, complete remission.

Table 2 Univariate analysis for OS

Variables	OS	
	HR (95% CI)	*P*-value
DOCK1 (high vs low)	2.940 (1.655–5.211)	<0.001
Age (≥60 vs <60 years)	1.406 (0.769–2.571)	0.268
WBC (≥30 vs <30×10^9/L)	0.986 (0.571–1.702)	0.959
Risk(poor vs non-poor)	1.290 (0.719–2.313)	0.393
FLT3-ITD (negative vs positive)	0.600 (0.319–1.131)	0.114
NPM1 (wild vs mutated)	1.243 (0.651–2.372)	0.510
DNMT3A (wild vs mutated)	0.794 (0.421–1.498)	0.477
CEBPA double mutation	0.656 (0.159–2.705)	0.559
IDH1/2 (wild vs mutated)	1.275 (0655–2.483)	0.475
RUNX1 (wild vs mutated)	0.410 (0.190–0.887)	0.024
Transplant in CR1/2 (yes vs no)	0.615 (0.337–1.124)	0.114

Abbreviations: OS, overall survival; WBC, white blood cell; CR, complete remission.

Table 3 Multivariate analysis for OS

Variables	OS	
	HR (95% CI)	*P*-value
DOCK1 (high vs low)	3.027 (1.304–7.025)	0.010
Age (≥60 vs <60 years)	0.977 (0.492–1.942)	0.947
WBC (≥30 vs <30×10^9/L)	0.615 (0.291–1.300)	0.203
Risk (poor vs non-poor)	1.282 (0.605–2.717)	0.517
FLT3-ITD (negative vs positive)	0.435 (0.183–1.036)	0.060
NPM1 (wild vs mutated)	1.285 (0.483–3.422)	0.616
DNMT3A (wild vs mutated)	0.479 (0.216–1.064)	0.071
CEBPA double mutation	2.519 (0.456–13.908)	0.289
IDH1/2 (wild vs mutated)	0.921 (0.351–2.416)	0.867
RUNX1 (wild vs mutated)	0.725 (0.257–2.045)	0.543
Transplant in CR1/2 (yes vs no)	0.459 (0.216–0.976)	0.043

Abbreviations: OS, overall survival; WBC, white blood cell; CR, complete remission.

In conclusion, higher *DOCK1* expression could predict a worse outcome in AML patients and its effect could not be overcome by allo-HSCT. *DOCK1* is a potential anti-leukemia target for AML treatment.

Ethics approval and consent to participate

The study was approved by the Human Research Ethics Committee of Washington University. Informed consent was obtained from all the participants.

Availability of data and materials

All the data in this study were generated by TCGA database.

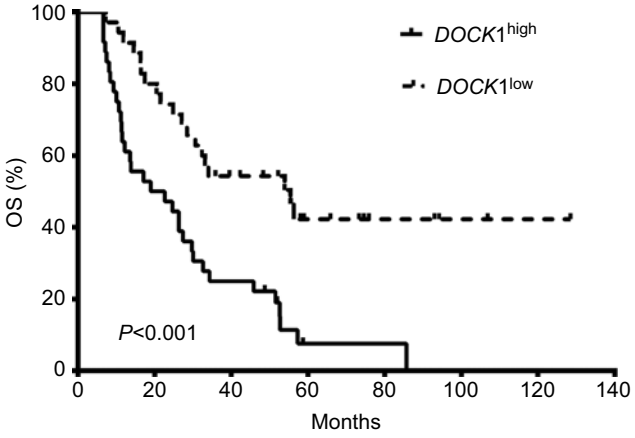

Figure 1 Kaplan–Meier curves of overall survival (OS). Patients in *DOCK1*^{high} group have shorter OS than those in *DOCK1*^{low} group.

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Author contributions

Lin Fu and Xiaoyan Ke designed the study and substantially contributed to the overall analysis of the study. Gaoqi Zhang wrote the manuscript. Jinlong Shi organized the data. Xinrui Yang, Xinpei Zhang, Jilei Zhang, Siyuan Yang and Jing Wang performed statistical analyses and analyzed the data. Jilei Zhang provided guidance on modification. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Short NJ, Rytting ME, Cortes JE. Acute myeloid leukaemia. *Lancet*. 2018. doi:10.1016/S0140-6736(18)31041-9
2. Barbui T, Thiele J, Gisslinger H, *et al*. The 2016 WHO classification and diagnostic criteria for myeloproliferative neoplasms: document summary and in-depth discussion. *Blood Cancer J*. 2018;8(2):15. doi:10.1038/s41408-018-0054-y
3. Dohner H, Estey E, Grimwade D, *et al*. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129(4):424–447. doi:10.1182/blood-2016-08-733196

4. Gale RE, Green C, Allen C, *et al*. The impact of FLT3 internal tandem duplication mutant level, number, size, and interaction with NPM1 mutations in a large cohort of young adult patients with acute myeloid leukemia. *Blood*. 2008;111(5):2776–2784. doi:10.1182/blood-2007-08-109090
5. Taskesen E, Bullinger L, Corbacioglu A, *et al*. Prognostic impact, concurrent genetic mutations, and gene expression features of AML with CEBPA mutations in a cohort of 1182 cytogenetically normal AML patients: further evidence for CEBPA double mutant AML as a distinctive disease entity. *Blood*. 2011;117(8):2469–2475. doi:10.1182/blood-2010-09-307280
6. Rakheja D, Konoplev S, Medeiros LJ, Chen W. IDH mutations in acute myeloid leukemia. *Hum Pathol*. 2012;43(10):1541–1551. doi:10.1016/j.humpath.2012.05.003
7. Bowen D, Groves MJ, Burnett AK, *et al*. TP53 gene mutation is frequent in patients with acute myeloid leukemia and complex karyotype, and is associated with very poor prognosis. *Leukemia*. 2009;23(1):203–206. doi:10.1038/leu.2008.173
8. Gaidzik VI, Bullinger L, Schlenk RF, *et al*. RUNX1 mutations in acute myeloid leukemia: results from a comprehensive genetic and clinical analysis from the AML study group. *J Clin Oncol*. 2011;29(10):1364–1372. doi:10.1200/JCO.2010.30.7926
9. Schlenk RF. Post-remission therapy for acute myeloid leukemia. *Haematologica*. 2014;99(11):1663–1670. doi:10.3324/haematol.2014.114611
10. Koreth J, Schlenk R, Kopecky KJ, *et al*. Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: systematic review and meta-analysis of prospective clinical trials. *JAMA*. 2009;301(22):2349–2361. doi:10.1001/jama.2009.813
11. Kihara R, Nagata Y, Kiyoi H, *et al*. Comprehensive analysis of genetic alterations and their prognostic impacts in adult acute myeloid leukemia patients. *Leukemia*. 2014;28(8):1586–1595. doi:10.1038/leu.2014.55
12. Yanada M, Mori J, Aoki J, *et al*. Effect of cytogenetic risk status on outcomes for patients with acute myeloid leukemia undergoing various types of allogeneic hematopoietic cell transplantation: an analysis of 7812 patients. *Leuk Lymphoma*. 2018;59(3):601–609. doi:10.1080/10428194.2017.1357173
13. Takami A. Hematopoietic stem cell transplantation for acute myeloid leukemia. *Int J Hematol*. 2018;107(5):513–518. doi:10.1007/s12185-018-2412-8
14. Rashidi A, Linden MA, DeFor TE, *et al*. History of consolidation is prognostic in acute myeloid leukemia patients undergoing allogeneic hematopoietic cell transplantation in minimal residual disease-negative first complete remission. *Am J Hematol*. 2017;92(10):1032–1036. doi:10.1002/ajh.24834
15. Araki D, Wood BL, Othus M, *et al*. Allogeneic hematopoietic cell transplantation for Acute myeloid leukemia: time to move toward a minimal residual disease-based definition of complete remission? *J Clin Oncol*. 2016;34(4):329–336. doi:10.1200/JCO.2015.63.3826
16. Chen DJ, Chen W, Jiang H, Yang H, Wang YC, Chen JH. Downregulation of DOCK1 sensitizes bladder cancer cells to cisplatin through preventing epithelial-mesenchymal transition. *Drug Des Devel Ther*. 2016;10:2845–2853. doi:10.2147/DDDT.S101998
17. Gadea G, Blangy A. Dock-family exchange factors in cell migration and disease. *Eur J Cell Biol*. 2014;93(10–12):466–477. doi:10.1016/j.ejcb.2014.06.003
18. Laurin M, Huber J, Pelletier A, *et al*. Rac-specific guanine nucleotide exchange factor DOCK1 is a critical regulator of HER2-mediated breast cancer metastasis. *Proc Natl Acad Sci U S A*. 2013;110(18):7434–7439. doi:10.1073/pnas.1213050110
19. Lee SH, Chiu YC, Li YH, *et al*. High expression of dedicator of cytokinesis 1 (DOCK1) confers poor prognosis in acute myeloid leukemia. *Oncotarget*. 2017;8(42):72250–72259. doi:10.18632/oncotarget.19706
20. Zhang J, Shi J, Zhang G, *et al*. BAALC and ERG expression levels at diagnosis have no prognosis impact on acute myeloid leukemia patients undergoing allogeneic hematopoietic stem cell transplantation. *Ann Hematol*. 2018;97(8):1391–1397. doi:10.1007/s00277-018-3331-8
21. Chou SC, Tang JL, Hou HA, *et al*. Prognostic implication of gene mutations on overall survival in the adult acute myeloid leukemia patients receiving or not receiving allogeneic hematopoietic stem cell transplantations. *Leuk Res*. 2014;38(11):1278–1284. doi:10.1016/j.leukres.2014.08.012
22. Ma Y, Wu Y, Shen Z, Zhang X, Zeng D, Kong P. Is allogeneic transplantation really the best treatment for FLT3/ITD-positive acute myeloid leukemia? A systematic review. *Clin Transplant*. 2015;29(2):149–160. doi:10.1111/ctr.12495
23. Xu Y, Sun Y, Shen H, *et al*. Allogeneic hematopoietic stem cell transplantation could improve survival of cytogenetically normal adult acute myeloid leukemia patients with DNMT3A mutations. *Am J Hematol*. 2015;90(11):992–997. doi:10.1002/ajh.24135
24. Grimsley CM, Kinchen JM, Tosello-Trampont A-C, et al. Dock180 and ELMO1 proteins cooperate to promote evolutionarily conserved Rac-dependent cell migration. *J Biol Chem*. 2004;279(7):6087–6097. doi:10.1074/jbc.M307087200
25. Jarzynka MJ, Hu B, Hui KM, *et al*. ELMO1 and Dock180, a bipartite Rac1 guanine nucleotide exchange factor, promote human glioma cell invasion. *Cancer Res*. 2007;67(15):7203–7211. doi:10.1158/0008-5472.CAN-07-0473
26. Jing X, Wu H, Ji X, Wu H, Shi M, Zhao R. Cortactin promotes cell migration and invasion through upregulation of the dedicator of cytokinesis 1 expression in human colorectal cancer. *Oncol Rep*. 2016;36(4):1946–1952. doi:10.3892/or.2016.5058
27. Tajiri H, Uruno T, Shirai T, *et al*. Targeting ras-driven cancer cell survival and invasion through selective inhibition of DOCK1. *Cell Rep*. 2017;19(5):969–980. doi:10.1016/j.celrep.2017.04.016

Supplementary materials

We analyze the relapse-free survival (RFS) rate using the univariate and multivariate analysis. The log-rank test was used to analyze significant differences between survival distributions. A cox proportional hazard model was applied to univariable and multivariable analyses to assess possible prognostic factors. *DOCK1* expression did not show any significant effect on RFS outcome in uni- and multivariate analysis (Tables S1 and S2). The Kaplan–Meier curve of RFS showed no significance either (Figure S1).

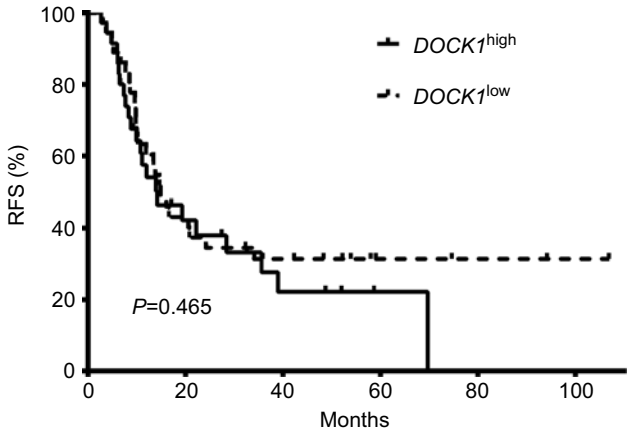

Figure S1 Kaplan–Meier curves of relapse-free survival (RFS). There is no difference between *DOCK1*^{high} group and *DOCK1*^{low} group in the length of RFS.

Table S1 Univariate analysis for RFS

Variables	RFS	
	HR (95% CI)	*P*-value
DOCK1 (high vs low)	1.264 (0.716-2.233)	0.419

Abbreviations: RFS, relapse-free survival; CR, complete remission.

Table S2 Multivariate analysis for RFS

Variables	RFS	
	HR (95% CI)	*P*-value
DOCK1 (high vs low)	1.242 (0.585–2.634)	0.573
Age (≥60 vs <60 years)	0.620 (0.276–1.392)	0.247
WBC (≥30 vs <30×10^9/L)	1.832 (0.884–3.799)	0.104
Risk (poor vs non-poor)	0.771 (0.353-1.686)	0.515
FLT3-ITD (negative vs positive)	0.502 (0.237–1.061)	0.071
NPM1 (wild vs mutated)	1.910 (0.807–4.520)	0.141
DNMT3A (wild vs mutated)	0.981 (0.448–2.146)	0.961
CEBPA double mutation	0.474 (0.092–2.450)	0.373
IDH1/2 (wild vs mutated)	1.002 (0.372–2.700)	0.996
RUNX1 (wild vs mutated)	1.139 (0.319–4.061)	0.841
Transplant in CR1/2 (yes vs no)	0.866 (0.409–1.832)	0.707

Abbreviations: RFS, relapse-free survival; WBC, white blood cell; CR, complete remission.