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Prognostic effect of allogeneic hematopoietic stem cell transplantation on first and non-first complete remission in acute myeloid leukemia

Ning Hu¹, Zhiheng Cheng², Yifan Pang³, Hongmian Zhao¹, Hui Ding¹, Li Chen¹, Qianyu Li¹, Yu Han¹, Tong Qin¹, Yifeng Dai², Yijie Zhang⁴, Jinlong Shi⁵, Depei Wu⁶, Lin Fu^{1,7,8}

¹Department of Hematology, Huaihe Hospital of Henan University, Kaifeng 475000, China; ²Department of Pathology and Medical Biology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; ³Department of Medicine, William Beaumont Hospital, Royal Oak, MI, USA; ⁴Department of Respiratory, Huaihe Hospital of Henan University, Kaifeng 475000, China; ⁵Department of Biomedical Engineering, Chinese PLA General Hospital, Beijing 100853, China; ⁶Department of Hematology, The First Affiliated Hospital of Soochow University, Suzhou 215006, China; ⁷Department of Hematology, ⁸Translational Medicine Center, The Second Affiliated Hospital of Guangzhou Medical University, Guangzhou 510260, China

Correspondence to: Lin Fu, MD, PhD. Department of Hematology, The Second Affiliated Hospital of Guangzhou Medical University, Guangzhou 510260, China. Email: fulin022@126.com.

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Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is considered the cure for intermediate or adverse-risk acute myeloid leukemia (AML) (1). It offers patients longer overall survival (OS) (2-4). Unfortunately, human leukocyte antigen (HLA) matched related donor is unavailable in more than 70% patients. Some of these patients, may experience relapse and subsequently achieve CR (non-CR1) with treatment. Some non-CR1 patients eventually receive allo-HSCT. It is unclear whether allo-HSCT will improve the survival of these patients.

We collected 53 AML patients from The Cancer Genome Atlas (TCGA) database (<https://cancergenome.nih.gov/>) to determine whether prognosis was different between CR1 and non-CR1 AML patients following allo-HSCT (5). All patients were between ages 22 and 69, registered between November 2001 and March 2010. Non-CR1 was defined as complete remission after two or more relapse treatments. These data were used to assess prognostic criteria according to the recent European Leukemia Net (ELN) classification (6). OS was the study endpoint and was defined as the time from diagnosis to death or censoring at the last follow-up.

Clinical characteristics of the CR1 group (n=32) and the non-CR1 group (n=21) were summarized in *Table 1*. The

median age of the CR1 group was significantly older than non-CR1 group (57.5 *vs.* 48, $P=0.031$); the CR1 group also had more patients older than 60 years (23 *vs.* 3, $P=0.014$). There were more favorable-risk patients in the non-CR1 group ($P<0.001$). No significant differences was found in the type of donor between CR1 and non-CR1 groups.

Kaplan-Meier survival curves showed that there was no significant difference in OS between the CR1 and non-CR1 groups (*Figure 1*). We also assessed the prognostic significance of clinical and molecular characteristic, including remission status, risk category, age, peripheral WBC count, *FLT3-ITD*, *NPM1* and *DNMT3A* with multivariate analysis (*Table 2*). The results indicated that none of these factors had any impact on OS.

We included the clinical features with significant differences between the two groups in *Table 1* and typical prognostic factors into a multivariate analysis, and found no significant difference in OS between the CR1 group and the non-CR1 group (*Table 2*).

In this study, we found that there was no prognostic difference between CR1 and non-CR1 patients following allo-HSCT. Allo-HSCT might weaken the adverse effect of relapse in non-CR1 patients and should still be offered once consequential remission was achieved.

Table 1 Comparison of clinical characteristics of the CR1 and the non-CR1 group

Characteristic	CR1 (n=32)	Non-CR1 (n=21)	Statistics	P value
CR subtypes/n (%)				
CR2	0 (0.0)	16 (76.2)	$\chi^2=34.924^{\S}$	0
CR3	0 (0.0)	3 (14.3)	$\chi^2=4.846^{\S}$	0.028
CR4	0 (0.0)	1 (4.8)	$\chi^2=1.553^{\S}$	0.213
> CR4	0 (0.0)	1 (4.8)	$\chi^2=1.553^{\S}$	0.213
Age/years, median (range)	57.5 [22–69]	48 [23–65]	U=217.5*	0.031
Age group/n (%)				
<60 years	19 (59.4)	19 (90.5)	$\chi^2=6.044^{\S}$	0.014
≥60 years	13 (40.6)	2 (9.5)		
Gender/n (%)				
Female	12 (37.5)	10 (47.6)	$\chi^2=0.535^{\S}$	0.465
Male	20 (62.5)	11 (52.4)		
WBC count/ $\times 10^9/L$, median (range)				
	11.95 (0.6–118.8)	33.2 (1.5–223.8)	U=231.5*	0.057
<40	24 (75.0)	13 (61.9)	$\chi^2=1.032^{\S}$	0.310
≥40	8 (25.0)	8 (38.1)		
BM blasts/%, median (range)				
	64 [30–99]	75 [34–97]	U=270*	0.230
<50	7 (21.9)	3 (14.3)	$\chi^2=0.477^{\S}$	0.490
≥50	25 (78.1)	18 (85.7)		
FAB subtypes/n (%)				
M0	4 (12.5)	2 (9.5)	$\chi^2=0.112^{\S}$	1
M1	7 (21.9)	6 (28.6)	$\chi^2=0.307^{\S}$	0.579
M2	10 (31.2)	3 (14.3)	$\chi^2=1.971^{\S}$	0.204
M3	0 (0.0)	3 (14.3)	$\chi^2=4.846^{\S}$	0.057
M4	6 (18.8)	6 (28.6)	$\chi^2=0.698^{\S}$	0.507
M5	3 (9.4)	1 (4.8)	$\chi^2=0.387^{\S}$	1
M6	1 (3.1)	0 (0.0)	$\chi^2=0.669^{\S}$	1
M7	1 (3.1)	0 (0.0)	$\chi^2=0.669^{\S}$	1
Risk category/n (%)				
Favorable	0 (0.0)	8 (38.1)	$\chi^2=14.358^{\S}$	0
Intermediate	18 (56.3)	10 (47.6)	$\chi^2=0.379^{\S}$	0.538
Adverse	13 (40.6)	3 (14.3)	$\chi^2=4.174^{\S}$	0.066
HSCT				
Haplo	0 (0.0)	0 (0.0)		
Sib allo	19 (59.4)	8 (38.1)	$\chi^2=2.297^{\S}$	0.166
MUD	13 (41.6)	13 (61.9)	$\chi^2=2.297^{\S}$	0.166

*, denotes Mann-Whitney U test; \S , denotes chi-square test. CR, complete remission; FAB, French-American-British; WBC, white blood cell; BM, bone marrow; PB, peripheral blood; HSCT, hematopoietic stem cell transplantation.

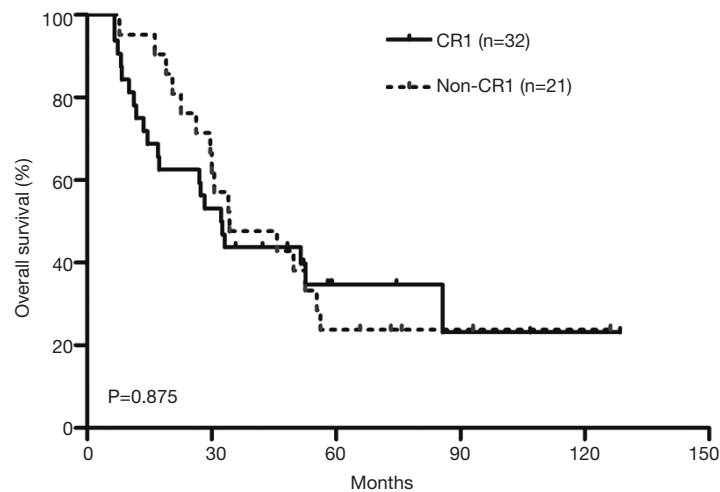


Figure 1 Kaplan-Meier curves of OS. No significant difference was found in OS between CR1 and non-CR1. P value was estimated by the log-rank test.

Table 2 Uni- and multivariate analyses for OS based on allo-HSCT

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Remission status (CR1 vs. non-CR1)	1.053 (0.549–2.021)	0.876	0.751 (0.33–1.804)	0.522
Risk category (favorable/intermediate vs. adverse)	1.291 (0.634–2.629)	0.482	0.613 (0.251–1.499)	0.283
Age (<60 vs. ≥60 years)	0.643 (0.322–1.285)	0.212	0.574 (0.26–1.264)	0.168
WBC (<40 vs. ≥40×10 ⁹ /L)	0.731 (0.365–1.464)	0.376	0.926 (0.349–2.457)	0.877
<i>FLT3-ITD</i> (positive vs. negative)	0.686 (0.312–1.508)	0.348	0.575 (0.200–1.648)	0.303
<i>NPM1</i> (mutated vs. wild type)	0.919 (0.418–2.020)	0.834	1.265 (0.429–3.736)	0.670
<i>DNMT3A</i> (mutated vs. wild type)	0.803 (0.376–1.714)	0.571	0.693 (0.264–1.817)	0.456

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

The optimum timing for allo-HSCT in AML patients remains controversial. A previous study found that AML patients who did not receive a transplant in CR1, but underwent allo-HSCT in CR2 had superior survival compared with the patients who did not undergo allo-HSCT, particularly in the intermediate-risk patients (7). Compared with this study, our research found no difference in adult AML patients who underwent allo-HSCT in CR1 or subsequent CR, providing some insight into the timing to perform transplantation.

Our study was limited by its small sample size. The favorable risk patients are exclusively included in non

CR1 series because they were considered for allogeneic HSCT only in case of AML relapse. Furthermore, the baseline characteristics of the CR1 group and the non-CR1 group were not balanced, with older patients in the CR1 group, and more good-risk patients in the non-CR1 group, which could have affected the results. Nevertheless, our study showed the same prognosis in CR1 and non-CR1 patients following allo-HSCT, and supported that allo-HSCT was a reasonable post-remission therapy in adult AML patients who had reached another CR after relapse from CR1. Further studies with larger cohorts are warranted to validate our findings.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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