The prognostic benefit from intermediate-dose cytarabine as consolidation therapy varies by cytogenetic subtype in t(8;21) acute myeloid leukemia: a retrospective cohort study

Guofeng Chen[1#^], Jiaqi Yang[2#], Fuliang Cao[1#], Wei Zhou[3,4], Dan Gong[5], Liren Liu[2], Dejun Zhou[1^]

[1]Department of Endoscopy, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Molecular Cancer Epidemiology of Tianjin, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Center for Cancer, Tianjin, China; [2]Department of Molecular Pharmacology, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Molecular Cancer Epidemiology of Tianjin, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Center for Cancer, Tianjin, China; [3]Central Laboratory, Shenzhen University General Hospital, Shenzhen, China; [4]Guangdong Key Laboratory for Biomedical Measurements and Ultrasound Imaging, School of Biomedical Engineering, Shenzhen University Health Science Center, Shenzhen, China; [5]Department of Hematology, Chinese PLA No. 965 Hospital, Jilin, China

Contributions: (I) Conception and design: G Chen, J Yang, F Cao, L Liu, D Zhou; (II) Administrative support: L Liu, D Zhou; (III) Provision of study materials or patients: G Chen, W Zhou, D Gong; (IV) Collection and assembly of data: J Yang, F Cao; (V) Data analysis and interpretation: G Chen, J Yang, F Cao, L Liu, D Zhou; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Liren Liu; Dejun Zhou. Tianjin Medical University Cancer Institute and Hospital, Hexi District, Tianjin 300060, China. Email: liuliren@tjmuch.com; zhoudejun@tjmuch.com.

Background: Patients with different karyotypes had different prognosis in t(8;21) acute myeloid leukemia (AML). Cytarabine (Ara-C) plays an important role as consolidation therapy in t(8;21) AML. T(8;21) AML patients with different karyotypes responded differently to post-remission therapy with Ara-C. However, the optimum dose of Ara-C in patients with different karyotypes remains unclear.

Methods: From January 2002 to September 2018, a total of 188 younger adult (14–60 years) patients with t(8;21) AML were enrolled in this retrospective study. Cytogenetic analysis and aberration descriptions followed the International System for Human Cytogenetic Nomenclature. All the patients achieved first complete remission (CR1) after induction chemotherapy. Patients received low-dose Ara-C [LDAC (<1 g/m^2)], intermediate-dose Ara-C [IDAC (1–1.5 g/m^2)], or high-dose Ara-c [HiDAC (2–3 g/m^2)] regimens as consolidation therapy after CR1. All patients were followed for survival or relapse until death, or study completion. We analyzed the prognosis of LDAC, IDAC, and HiDAC regimens as consolidation therapy in patients with different karyotypes. The primary endpoint was overall survival (OS) and the secondary endpoint was relapse-free survival (RFS).

Results: The results showed IDAC significantly improved OS compared with LDAC [hazard rate (HR) =0.55, P=0.0375] when the clinical factors were adjusted. However, no significant difference between HiDAC and IDAC was found. Subgroup analysis further showed that the OS advantage of IDAC was focused on patients with additional cytogenetic abnormalities, including loss of X chromosome (-X), del(9q), or complex karyotype (group B, HR =0.21, P=0.0125), but not on patients with t(8;21)-only or additional loss of Y chromosome (-Y) cytogenetics (group A, HR =0.77, P=0.4804) in multivariate analysis. Similarly, better OS was shown after IDAC than LDAC consolidation in patients in group B, whether they received allogeneic hematopoietic stem cell transplantation (allo-HSCT) or not, but not in group A.

Conclusions: IDAC was suitable for patients with additional -X, del(9q), or complex karyotype, while LDAC might be sufficient for patients with t(8;21)-only or additional -Y cytogenetics. It suggested that t(8;21) AML patients with different karyotypes should use different consolidation regimens.

^ ORCID: Guofeng Chen, 0000-0002-9558-746X; Dejun Zhou, 0000-0003-4238-5773.

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Introduction

The World Health Organization (WHO) categorizes acute myeloid leukemia (AML) with t(8;21) as an individual AML disease (1,2). Compared with other AML subtypes, T(8;21) AML is associated with superior outcomes and survival. However, patients with t(8;21) AML have considerable clinical heterogeneity, with a relapse rate of up to 40% and probability of overall survival (OS) between 40–60% (3-5).

Cytarabine (Ara-C) has been used as a consolidation therapy for AML for 40 years (6,7). However, there is uncertainty regarding the optimal dose of Ara-C for consolidation therapy in AML. Some studies have shown a lower risk of relapse with high-dose cytarabine (HiDAC) consolidation, although this did not translate into an OS benefit (8,9). Other studies have found no better OS or relapse-free survival (RFS) after HiDAC consolidation (10-14). Consequently, we wondered whether HiDAC could improve outcomes in patients with t(8;21) AML.

Patients with t(8;21) AML show considerable additional cytogenetic abnormalities, such as loss of Y chromosome (-Y), loss of X chromosome (-X), del(9q), and complex karyotype. In t(8;21) AML, additional cytogenetic abnormalities were detected in more than 70% of patients (15-17). The additional cytogenetic aberrations have substantial influence on prognosis and clinical outcomes (18-22). In our previous studies, t(8;21) AML patients with additional -Y could not benefit from HiDAC regimen (1.5–3 g/m^2/12 h) (23), whereas for patients with additional -X, the HiDAC regimen was suitable (24). This suggested that t(8;21) AML patients with different karyotypes responded differently to post-remission therapy with Ara-C.

However, how patients with different karyotypes choose consolidation regimens remain unclear. Thus, we performed a retrospective study involving 15 Chinese AML centers. In this study, we compared low-dose Ara-C (LDAC), intermediate-dose Ara-C (IDAC), and HiDAC regimens in younger adult patients with different karyotypes. The aim of the present study was to assess the efficacy of post-remission therapy with different doses of Ara-C in patients with different karyotypes. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2965/rc).

Methods

Patients

Clinical data for 651 patients with t(8;21) AML between January 2002 and September 2018 were collected in this retrospective study. The data were obtained using special case report forms from 15 AML study groups (the First Affiliated Hospital of Jilin University, the 307 Hospital of PLA, the Navy General Hospital, the First Affiliated Hospital of Dalian Medical University, the First Affiliated Hospital of PLA General Hospital, the General Hospital of the Air Force, the Peking University Third Hospital, the Beijing Friendship Hospital, the China-Japan Friendship Hospital, the Second Affiliated Hospital of Hebei Medical University, the Affiliated Cancer Hospital of Zhengzhou University, the The First Affiliated Hospital of Harbin Medical University, the Shengjing Hospital of China Medical University, the Henan Provincial People's Hospital, and the Tianjin Medical University Cancer Institute and Hospital) in China. All participating centers were informed and agreed the study. The exclusion criteria for this study were as follows: (I) 37 patients with no treatment information; (II) 90 patients aged less than 14 years or more than 60 years; (III) 61 patients who failed to achieve first complete remission (CR1) after 1 or 2 courses of induction chemotherapy; (IV) 134 patients with missing cytogenetic reports; (V) 131 patients received other consolidation regimens; and (VI) 10 patients received autologous hematopoietic stem cell transplantation (HSCT). Ultimately, 188 cases were included in this study (*Figure 1*).

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Tianjin Medical University Cancer Institute and Hospital (No. bc2022154). Individual consent for this retrospective analysis was waived.

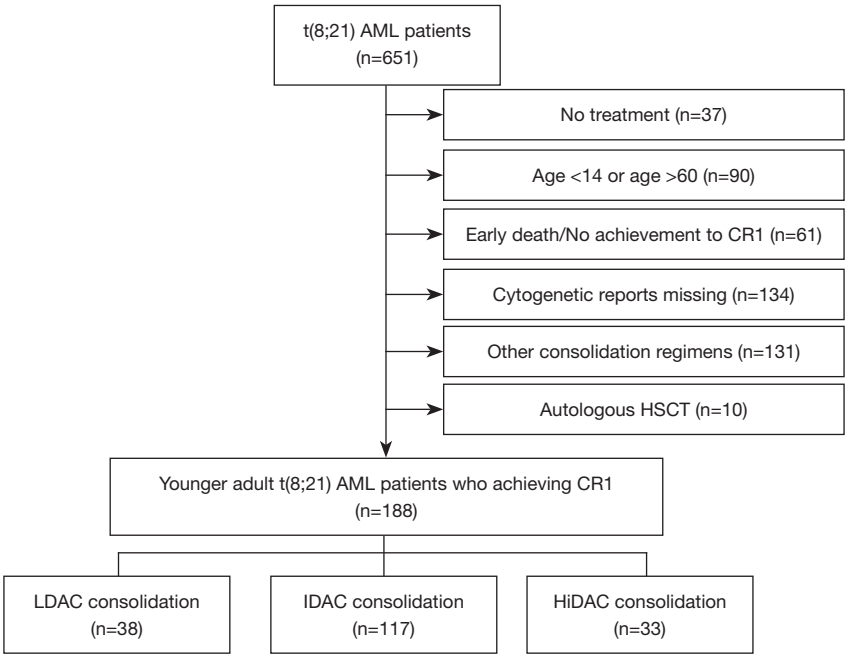

Figure 1 Study enrollment chart. AML, acute myeloid leukemia; CR1, first complete remission; HSCT, hematopoietic stem cell transplantation; LDAC, low-dose cytarabine; IDAC, intermediate-dose cytarabine; HiDAC, high-dose cytarabine.

Cytogenetic and molecular testing

Cytogenetic studies were carried out using standard techniques. The cytogenetic aberration descriptions followed the recommendations of the International System for Human Cytogenetic Nomenclature (25). Complex karyotype was defined as 3 or more chromosomal abnormalities (26). Gene mutations of FLT3-ITD and KIT mutation were detected by direct sequencing method. Overexpression of Wilms' tumor gene 1 (WT1) was defined as ≥250 copies/10^4 ABL and detected with the recommended real-time polymerase chain reaction assay (27).

Study design and treatment

The study was a retrospective, multicenter study conducted at 15 centers in China. Patients who achieved CR1 were enrolled and received LDAC, IDAC, or HiDAC regimens as consolidation therapy. All patients were followed for survival or relapse until death, or study completion. Induction treatment involved 1–2 cycles of DA (Ara-c 100–200 mg/m^2 every 12 hours for 7 days in combination with daunorubicin 45–90 mg/m^2/day for 3 days), IA (Ara-c 100–200 mg/m^2 every 12 hours for 7 days in combination with idarubicin 8–12 mg/m^2/day for 3 days), or MA (Ara-c 100–200 mg/m^2 every 12 hours for 7 days in combination with mitoxantrone 6–10 mg/m^2/day for 3 days). When CR1 occurred, patients received consolidation therapy, including LDAC, IDAC, and HiDAC. The LDAC regimen was defined as <1 g/m^2/day for 7 days, the IDAC regimen was defined as 1–1.5 g/m^2 every 12 hours for 3 days or 1–1.5 g/m^2/day for days 1–5 or 6, and the HiDAC regimen was defined as 2–3 g/m^2 every 12 hours for 3 days. Fifty-eight patients in our study received allogeneic HSCT (allo-HSCT).

Endpoints

OS was the primary endpoint, which was defined as the survival period from the date of diagnosis to the date of last follow-up or death (28). Complete remission (CR) was defined as bone marrow blasts <5%, absence of circulating blasts and blasts with Auer rods, absolute neutrophil count ≥1.0×10^9/L, platelet count ≥100×10^9/L, and absence of extramedullary disease (26). Relapse was defined as a recurrence of >5% bone marrow blasts, reappearance of blasts in the blood, or the development of extramedullary disease infiltrates at any site (26). RFS was measured from

the date of attaining CR1 until the first relapse, death, or the final follow-up day (28).

Statistical analysis

Comparisons of patient characteristics between the two groups were calculated using the Mann-Whitney U test for continuous data and the χ^2 test for categorical variables. OS and RFS curves were assessed using the Kaplan-Meier method and compared with the log-rank test. Univariate and multivariate analyses for OS and RFS were estimated by Cox regression analysis. Variables significant at P value <0.10 in univariable analyses were entered into an explorative multivariable model. We also adjusted for features that, when added to this model, changed the matched hazard ratio (HR) by at least 10%. All analyses were performed using Stata Statistical Software, version 15.1 (StataCorp., Armonk, NY, USA), R (version 3.3.3), and EmpowerStats (http://www.empowerstats.com; X & Y Solutions, Inc., Boston, MA, USA). Two-sided P value <0.05 was considered statistically significant.

Results

Patient characteristics

A total of 188 patients with t(8;21) AML were enrolled in this study. All enrolled patients achieved CR1 after induction. The median follow-up was 61.8 months (2.5–135.7 months). At the end of the last follow-up, 76 (40.43%) patients had died. The 5-year OS rate was 50.16%. Of the 188 patients, 85 (45.2%) patients had t(8;21)-only, 103 (54.8%) patients had additional cytogenetic abnormalities, including 41 (21.8%) patients with -Y, 23 (12.2%) patients with -X, 9 (4.8%) patients with del(9q), 27 (14.4%) patients with complex karyotype, and 3 (1.6%) patients with other abnormalities. Patient characteristics are shown in *Tables 1,2*.

HiDAC resulted in no better therapeutic benefit than IDAC as consolidation therapy in t(8;21) AML

In the entire t(8;21) cohort, compared with LDAC, better OS was shown for IDAC (P=0.0115), while HiDAC did not show better OS compared with IDAC (P=0.0678) (*Figure 2A*). In the univariate and multivariate analyses, similar outcomes were shown. The HR for OS was 0.49 (IDAC *vs.* LDAC, P=0.0067, *Table 3*) and 0.49 (HiDAC *vs.* LDAC, P=0.0604, *Table 3*) in the univariate analysis, and it was 0.55 (IDAC *vs.* LDAC, P=0.0375, *Table 4*) and 0.51 (HiDAC *vs.* LDAC, P=0.1013, *Table 4*) in the multivariate analysis. In addition, compared with IDAC, HiDAC had no association with better OS in univariate regression (HR =0.98, P=0.9520, *Table 3*), multivariate regression (HR =0.90, P=0.7856, *Table 4*), or Kaplan-Meier curves (P=0.9586, *Figure 2A*).

With respect to RFS, Kaplan-Meier curves showed no statistical difference among the LDAC/IDAC/HiDAC regimens (IDAC *vs.* LDAC, P=0.0984; HiDAC *vs.* LDAC, P=0.3877; HiDAC *vs.* IDAC, P=0.7419, *Figure 2B*). Similarly, there was no significant difference in RFS among the 3 regimens in either univariate analysis (IDAC *vs.* LDAC, HR =0.64, P=0.0684; HiDAC *vs.* LDAC, HR =0.71, P=0.3029; HiDAC *vs.* IDAC, HR =1.10, P=0.7487, *Table 5*) or multivariate analysis (IDAC *vs.* LDAC, HR =0.70, P=0.1806; HiDAC *vs.* LDAC, HR =0.73, P=0.3625; HiDAC *vs.* IDAC, HR =1.00, P=0.9962, *Table 6*).

Patients with different karyotypes responded differently to consolidation therapy

In patients with t(8;21)-only (P=0.5199, Figure S1A) and patients with additional -Y (P=0.9011, Figure S1B), there was no statistical difference in OS among the 3 different consolidation regimens (LDAC, IDAC, and HiDAC). However, in patients with additional -X (P=0.1480, Figure S1C), additional del(9q) (P=0.0862, Figure S1D), and complex karyotype (P=0.1422, Figure S1E), OS was better for the IDAC/HiDAC consolidation regimens than for LDAC, although the difference was not statistically significant.

We divided patients into group A (patients with t[8;21]-only or patients with additional -Y) and group B (patients with additional -X, del[9q], complex karyotype, or other cytogenetic abnormalities). As shown in *Table 1*, patient characteristics between group A and B were well matched, except that group B had more female patients. This difference was due to the fact that patients with additional -Y (group A) were only male, while patients with additional -X (group B) were only female. As illustrated in *Table 2*, patient characteristics were balanced among the 3 regimens in both group A and B, except for the distribution of age in group B (P<0.001). More details are shown in *Table 1* and *Table 2*.

In group A, there was no statistical difference in OS between the 3 regimens in the univariate model (IDAC *vs.* LDAC, HR =0.69, P=0.2624; HiDAC *vs.* LDAC, HR =0.76, P=0.5369; HiDAC *vs.* IDAC, HR =1.09, P=0.8219, *Table 3*),

Table 1 Clinical characteristics of t(8;21) AML patients according to cytogenetic status

Variables	Total (n=188)	Group A* (n=126)	Group B# (n=62)	P value
Age (years), n (%)				0.121
≤33$	94 (50.0)	68 (54.0)	26 (41.9)	
>33$	94 (50.0)	58 (46.0)	36 (58.1)	
Sex, n (%)				<0.001
Male	105 (55.9)	81 (64.3)	24 (38.7)	
Female	83 (44.1)	45 (35.7)	38 (61.3)	
WBC ($\times10^9$/L), n (%)				0.568
≤20	147 (78.2)	97 (77.0)	50 (80.6)	
>20	41 (21.8)	29 (23.0)	12 (19.4)	
HB (g/L), n (%)				0.172
≤100	150 (79.8)	97 (77.0)	53 (85.5)	
>100	38 (20.2)	29 (23.0)	9 (14.5)	
PLT ($\times10^9$/L), n (%)				0.215
≤20	63 (33.5)	46 (36.5)	17 (27.4)	
>20	125 (66.5)	80 (63.5)	45 (72.6)	
Blasts in BM (%)				0.145
≤60	137 (72.9)	96 (76.2)	41 (66.1)	
>60	51 (27.1)	30 (23.8)	21 (33.9)	
Extramedullary, n (%)				0.547
Negative	173 (92.0)	117 (92.9)	56 (90.3)	
Positive	15 (8.0)	9 (7.1)	6 (9.7)	
KIT mutation, n (%)				0.159
Negative	160 (85.1)	104 (82.5)	56 (90.3)	
Positive	28 (14.9)	22 (17.5)	6 (9.7)	
WT1 overexpression, n (%)				0.649
Negative	155 (82.4)	105 (83.3)	50 (80.6)	
Positive	33 (17.6)	21 (16.7)	12 (19.4)	
FLT3-ITD, n (%)				0.193
Negative	183 (97.3)	124 (98.4)	59 (95.2)	
Positive	5 (2.7)	2 (1.6)	3 (4.8)	
Courses to CR1, n (%)				0.267
1	139 (73.9)	91 (72.2)	48 (77.4)	
2	44 (23.4)	30 (23.8)	14 (22.6)	
≥3	5 (2.7)	5 (4.0)	0 (0.0)	
Allo-HSCT, n (%)				0.705
No	130 (69.1)	86 (68.3)	44 (71.0)	
Yes	58 (30.9)	40 (31.7)	18 (29.0)	

*, defined as patients with t(8;21)-only or additional loss of Y chromosome; #, defined as patients with additional loss of X chromosome, del(9q), or complex karyotype; $, the median age. AML, acute myeloid leukemia; WBC, white blood cell count; HB, hemoglobin; PLT, platelets; BM, bone marrow; CR1, first complete remission; allo-HSCT, allogeneic hematopoietic stem cell transplantation.

Table 2 Clinical characteristics of patients in group A* (n=126) and B# (n=62) according to cytarabine dose

Variables	Group A* (n=126)				Group B# (n=62)			
	LDAC (n=20)	IDAC (n=83)	HiDAC (n=23)	P value	LDAC (n=18)	IDAC (n=34)	HiDAC (n=10)	P value
Age (years), n (%)				0.741				<0.001
≤33$	10 (50.0)	44 (53.0)	14 (60.9)		10 (55.6)	7 (20.6)	9 (90.0)	
>33$	10 (50.0)	39 (47.0)	9 (39.1)		8 (44.4)	27 (79.4)	1 (10.0)	
Sex, n (%)				0.359				0.684
Male	11 (55.0)	57 (68.7)	13 (56.5)		6 (33.3)	13 (38.2)	5 (50.0)	
Female	9 (45.0)	26 (31.3)	10 (43.5)		12 (66.7)	21 (61.8)	5 (50.0)	
WBC ($\times10^9$/L), n (%)				0.286				0.646
≤20	18 (90.0)	61 (73.5)	18 (78.3)		15 (83.3)	28 (82.4)	7 (70.0)	
>20	2 (10.0)	22 (26.5)	5 (21.7)		3 (16.7)	6 (17.6)	3 (30.0)	
HB (g/L), n (%)				0.618				0.236
≤100	14 (70.0)	64 (77.1)	19 (82.6)		15 (83.3)	31 (91.2)	7 (70.0)	
>100	6 (30.0)	19 (22.9)	4 (17.4)		3 (16.7)	3 (8.8)	3 (30.0)	
PLT ($\times10^9$/L), n (%)				0.159				0.474
≤20	6 (30.0)	35 (42.2)	5 (21.7)		3 (16.7)	11 (32.4)	3 (30.0)	
>20	14 (70.0)	48 (57.8)	18 (78.3)		15 (83.3)	23 (67.6)	7 (70.0)	
Blasts in BM (%), n (%)				0.964				0.903
≤60	15 (75.0)	63 (75.9)	18 (78.3)		12 (66.7)	23 (67.6)	6 (60.0)	
>60	5 (25.0)	20 (24.1)	5 (21.7)		6 (33.3)	11 (32.4)	4 (40.0)	
Extramedullary, n (%)				0.329				0.457
Negative	18 (90.0)	76 (91.6)	23 (100.0)		15 (83.3)	32 (94.1)	9 (90.0)	
Positive	2 (10.0)	7 (8.4)	0 (0.0)		3 (16.7)	2 (5.9)	1 (10.0)	
KIT mutation, n (%)				0.150				0.771
Negative	16 (80.0)	72 (86.7)	16 (69.6)		17 (94.4)	30 (88.2)	9 (90.0)	
Positive	4 (20.0)	11 (13.3)	7 (30.4)		1 (5.6)	4 (11.8)	1 (10.0)	
WT1 overexpression, n (%)				0.305				0.486
Negative	19 (95.0)	67 (80.7)	19 (82.6)		13 (72.2)	28 (82.4)	9 (90.0)	
Positive	1 (5.0)	16 (19.3)	4 (17.4)		5 (27.8)	6 (17.6)	1 (10.0)	
FLT3-ITD, n (%)				0.467				0.649
Negative	20 (100.0)	82 (98.8)	22 (95.7)		17 (94.4)	33 (97.1)	9 (90.0)	
Positive	0 (0.0)	1 (1.2)	1 (4.3)		1 (5.6)	1 (2.9)	1 (10.0)	
Courses to CR1, n (%)				0.463				0.128
1	15 (75.0)	59 (71.1)	17 (73.9)		11 (61.1)	28 (82.4)	9 (90.0)	
2	3 (15.0)	21 (25.3)	6 (26.1)		7 (38.9)	6 (17.6)	1 (10.0)	
≥3	2 (10.0)	3 (3.6)	0 (0.0)					
Allo-HSCT, n (%)				0.467				0.990
No	16 (80.0)	55 (66.3)	15 (65.2)		13 (72.2)	24 (70.6)	7 (70.0)	
Yes	4 (20.0)	28 (33.7)	8 (34.8)		5 (27.8)	10 (29.4)	3 (30.0)	

*, defined as patients with t(8;21)-only or additional loss of Y chromosome; #, defined as patients with additional loss of X chromosome, del(9q), or complex karyotype; $, the median age. LDAC, low-dose cytarabine (<1 g/m^2); IDAC, intermediate-dose cytarabine (1–1.5 g/m^2); HiDAC, high-dose cytarabine (2–3 g/m^2); WBC, white blood cell count; HB, hemoglobin; PLT, platelets; BM, bone marrow; CR1, first complete remission; allo-HSCT, allogeneic hematopoietic stem cell transplantation.

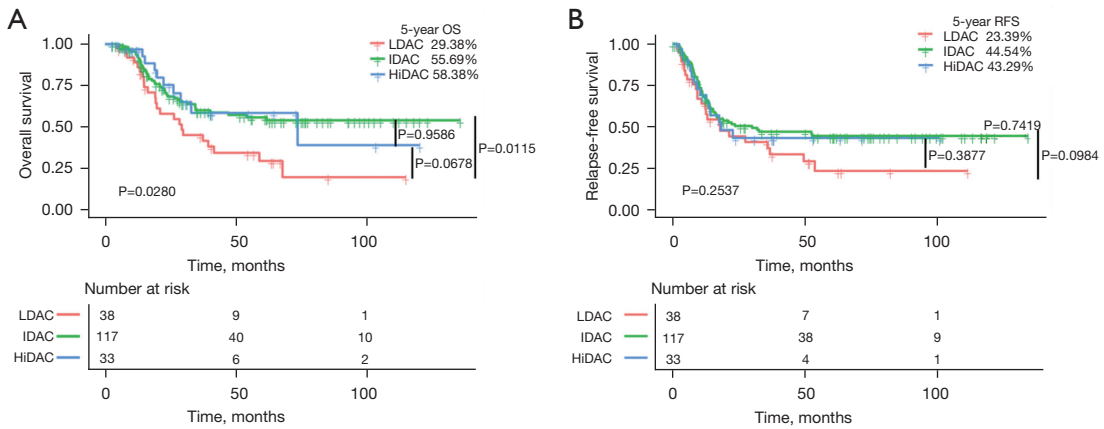

Figure 2 Prognostic impact of different doses of cytarabine in entire t(8;21) AML cohort. (A) OS; (B) RFS. LDAC, low-dose cytarabine; IDAC, intermediate-dose cytarabine; HiDAC, high-dose cytarabine; OS, overall survival; RFS, relapse-free survival.

Table 3 Univariate analysis of OS in the entire t(8;21) AML cohort (n=188), subcohort group A* (n=126), and subcohort B# (n=62)

Variables	Total (n=188)		Group A* (n=126)		Group B# (n=62)	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Consolidation						
LDAC	1.0		1.0		1.0	
IDAC	0.49 (0.30, 0.82)	0.0067	0.69 (0.36, 1.32)	0.2624	0.29 (0.11, 0.72)	0.0076
HiDAC	0.49 (0.23, 1.03)	0.0604	0.76 (0.32, 1.81)	0.5369	0.15 (0.02, 1.16)	0.0687
IDAC/HiDAC						
IDAC	1.0		1.0		1.0	
HiDAC	0.98 (0.49, 1.95)	0.9520	1.09 (0.52, 2.27)	0.8219	0.52 (0.07, 4.16)	0.5381
Age (years)						
≤33$	1.0		1.0		1.0	
>33$	0.97 (0.62, 1.54)	0.9121	1.06 (0.63, 1.80)	0.8174	0.79 (0.33, 1.91)	0.6027
Sex						
Male	1.0		1.0		1.0	
Female	0.86 (0.53, 1.39)	0.5475	0.93 (0.53, 1.63)	0.8053	0.74 (0.31, 1.79)	0.5053
WBC ($\times 10^9$/L)						
≤20	1.0		1.0		1.0	
>20	0.95 (0.56, 1.61)	0.8431	0.88 (0.48, 1.62)	0.6848	1.21 (0.40, 3.62)	0.7336
HB (g/L)						
≤100	1.0		1.0		1.0	
>100	1.14 (0.65, 1.98)	0.6534	1.14 (0.61, 2.13)	0.6797	1.14 (0.33, 3.91)	0.8300

Table 3 (*continued*)

Table 3 (*continued*)

Variables	Total (n=188)		Group A* (n=126)		Group B# (n=62)	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
PLT ($\times10^9$/L)						
≤20	1.0		1.0		1.0	
>20	0.69 (0.44, 1.09)	0.1079	0.75 (0.44, 1.27)	0.2884	0.54 (0.22, 1.32)	0.1773
Blasts in BM (%)						
≤60	1.0		1.0		1.0	
>60	1.42 (0.89, 2.28)	0.1412	1.32 (0.76, 2.30)	0.3200	1.65 (0.67, 4.05)	0.2715
Extramedullary						
Negative	1.0		1.0		1.0	
Positive	3.60 (1.93, 6.71)	<0.0001	2.68 (1.21, 5.96)	0.0155	6.10 (2.16, 17.23)	0.0006
KIT mutation						
Negative	1.0		1.0		1.0	
Positive	1.47 (0.80, 2.68)	0.2106	1.80 (0.94, 3.43)	0.0763	0.55 (0.07, 4.13)	0.5626
WT1 overexpression						
Negative	1.0		1.0		1.0	
Positive	0.66 (0.34, 1.29)	0.2237	0.66 (0.30, 1.46)	0.3076	0.68 (0.20, 2.34)	0.5443
FLT3-ITD						
Negative	1.0		1.0		1.0	
Positive	0.00 (0.00, Inf)	0.9959	0.00 (0.00, Inf)	0.9965	0.00 (0.00, Inf)	0.9979
Courses to CR1						
1	1.0		1.0		1.0	
2	2.91 (1.78, 4.73)	<0.0001	2.58 (1.45, 4.59)	0.0012	3.90 (1.55, 9.85)	0.0039
≥3	2.14 (0.51, 8.90)	0.2960	2.15 (0.51, 8.98)	0.2944	-	
Allo-HSCT						
No	1.0		1.0		1.0	
Yes	0.46 (0.26, 0.79)	0.0053	0.55 (0.29, 1.02)	0.0566	0.28 (0.08, 0.96)	0.0421

*, defined as patients with t(8;21)-only or additional loss of Y chromosome; #, defined as patients with additional loss of X chromosome, del(9q), or complex karyotype; $, the median age. OS, overall survival; AML, acute myeloid leukemia; LDAC, low-dose cytarabine (<1 g/m^2); IDAC, intermediate-dose cytarabine (1–1.5 g/m^2); HiDAC, high-dose cytarabine (2–3 g/m^2); WBC, white blood cell count; HB, hemoglobin; PLT, platelets; BM, bone marrow; CR1, first complete remission; allo-HSCT, allogeneic hematopoietic stem cell transplantation.

multivariate model (IDAC *vs.* LDAC, HR =0.77, P=0.4804; HiDAC *vs.* LDAC, HR =0.71, P=0.4846; HiDAC *vs.* IDAC, HR =0.88, P=0.7421, *Table 4*), or Kaplan-Meier curves (IDAC *vs.* LDAC, P=0.2736; HiDAC *vs.* LDAC, P=0.5508; HiDAC *vs.* IDAC, P=0.8216, *Figure 3A*).

In group B, there were significant differences in OS among the 3 different consolidation regimens (P=0.0053, *Figure 3B*). Individually, patients with IDAC (P=0.0042) or HiDAC (P=0.0347) consolidation had better OS than those with LDAC, while compared with IDAC, HiDAC did not show better OS (P=0.5308, *Figure 3B*). The 5-year survival rate for LDAC, IDAC, and HiDAC was 27.97%, 72.88%, and 88.89%, respectively (*Figure 3B*). Similar results were shown in

Table 4 Multivariate analysis of OS in the entire t(8;21) AML cohort (n=188), subcohort group A* (n=126), and subcohort B# (n=62)

Variables	Total (n=188)		Group A* (n=126)		Group B# (n=62)	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Consolidation						
LDAC	1.0		1.0		1.0	
IDAC	0.55 (0.31, 0.97)	0.0375	0.77 (0.37, 1.60)	0.4804	0.21 (0.06, 0.71)	0.0125
HiDAC	0.51 (0.23, 1.14)	0.1013	0.71 (0.28, 1.83)	0.4846	0.08 (0.01, 0.95)	0.0457
IDAC/HiDAC						
IDAC	1.0		1.0		1.0	
HiDAC	0.90 (0.44, 1.86)	0.7856	0.88 (0.40, 1.92)	0.7421	1.87 (0.21, 16.65)	0.5764
Sex						
Male	1.0		1.0		1.0	
Female	0.91 (0.54, 1.52)	0.7102	1.13 (0.62, 2.06)	0.6815	0.49 (0.17, 1.42)	0.1905
WBC ($\times10^9$/L)						
≤20	1.0		1.0		1.0	
>20	1.22 (0.70, 2.12)	0.4889	1.30 (0.68, 2.48)	0.4299	1.54 (0.38, 6.25)	0.5425
HB (g/L)						
≤100	1.0		1.0		1.0	
>100	1.12 (0.60, 2.08)	0.7238	1.29 (0.65, 2.56)	0.4714	0.49 (0.10, 2.45)	0.3865
PLT ($\times10^9$/L)						
≤20	1.0		1.0		1.0	
>20	0.52 (0.31, 0.87)	0.0133	0.66 (0.37, 1.19)	0.1696	0.28 (0.09, 0.87)	0.0279
Extramedullary						
Negative	1.0		1.0		1.0	
Positive	2.68 (1.27, 5.63)	0.0093	2.11 (0.83, 5.32)	0.1155	7.37 (1.77, 30.63)	0.0060
KIT mutation						
Negative	1.0		1.0		1.0	
Positive	1.63 (0.81, 3.27)	0.1729	2.06 (0.97, 4.36)	0.0591	0.98 (0.09, 11.19)	0.9864
WT1 overexpression						
Negative	1.0		1.0		1.0	
Positive	0.55 (0.27, 1.10)	0.0883	0.43 (0.18, 1.01)	0.0523	0.52 (0.11, 2.41)	0.4064
Courses to CR1						
1	1.0		1.0		1.0	
2	3.27 (1.92, 5.59)	<0.0001	4.09 (2.13, 7.88)	<0.0001	1.57 (0.41, 6.04)	0.5117
≥3	1.18 (0.26, 5.32)	0.8261	1.52 (0.33, 7.09)	0.5936	1.0	
Allo-HSCT						
No	1.0		1.0		1.0	
Yes	0.58 (0.32, 1.03)	0.0649	0.60 (0.30, 1.17)	0.1315	0.28 (0.07, 1.16)	0.0798

*, defined as patients with t(8;21)-only or additional loss of Y chromosome; #, defined as patients with additional loss of X chromosome, del(9q), or complex karyotype. OS, overall survival; AML, acute myeloid leukemia; LDAC, low-dose cytarabine (<1 g/m^2); IDAC, intermediate-dose cytarabine (1–1.5 g/m^2); HiDAC, high-dose cytarabine (2–3 g/m^2); WBC, white blood cell count; HB, hemoglobin; PLT, platelets; CR1, first complete remission; allo-HSCT, allogeneic hematopoietic stem cell transplantation.

Table 5 Univariate analysis of RFS in the entire t(8;21) AML cohort (n=188), subcohort group A* (n=126), and subcohort B# (n=62)

Variables	Total (n=188)		Group A* (n=126)		Group B# (n=62)	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Consolidation						
LDAC	1.0		1.0		1.0	
IDAC	0.64 (0.40, 1.03)	0.0684	0.73 (0.39, 1.36)	0.3208	0.52 (0.24, 1.15)	0.1069
HiDAC	0.71 (0.37, 1.36)	0.3029	0.78 (0.35, 1.74)	0.5433	0.65 (0.21, 2.03)	0.4556
IDAC/HiDAC						
IDAC	1.0		1.0		1.0	
HiDAC	1.10 (0.62, 1.94)	0.7487	1.05 (0.54, 2.04)	0.8903	1.24 (0.41, 3.79)	0.7032
Age, years						
≤33$	1.0		1.0		1.0	
>33$	0.88 (0.58, 1.31)	0.5228	0.99 (0.61, 1.60)	0.9544	0.64 (0.31, 1.33)	0.2307
Sex						
Male	1.0		1.0		1.0	
Female	0.81 (0.53, 1.24)	0.3247	1.04 (0.63, 1.71)	0.8905	0.48 (0.23, 1.00)	0.0500
WBC ($\times10^9$/L)						
≤20	1.0		1.0		1.0	
>20	0.88 (0.55, 1.42)	0.6051	0.87 (0.50, 1.51)	0.6233	0.93 (0.35, 2.44)	0.8808
HB (g/L)						
≤100	1.0		1.0		1.0	
>100	1.25 (0.77, 2.02)	0.3651	1.16 (0.67, 2.02)	0.5921	1.58 (0.60, 4.16)	0.3524
PLT ($\times10^9$/L)						
≤20	1.0		1.0		1.0	
>20	0.81 (0.53, 1.22)	0.3043	0.93 (0.57, 1.52)	0.7748	0.54 (0.26, 1.15)	0.1123
Blasts in BM (%)						
≤60	1.0		1.0		1.0	
>60	1.45 (0.94, 2.21)	0.0897	1.47 (0.88, 2.45)	0.1391	1.43 (0.66, 3.08)	0.3641
Extramedullary						
Negative	1.0		1.0		1.0	
Positive	2.87 (1.56, 5.29)	0.0007	2.22 (1.01, 4.88)	0.0476	4.36 (1.62, 11.71)	0.0035
KIT mutation						
Negative	1.0		1.0		1.0	
Positive	1.52 (0.88, 2.60)	0.1305	1.81 (1.00, 3.28)	0.0495	0.71 (0.17, 2.98)	0.6384
WT1 overexpression						
Negative	1.0		1.0		1.0	
Positive	0.63 (0.34, 1.15)	0.1305	0.77 (0.38, 1.56)	0.4673	0.40 (0.12, 1.33)	0.1353

Table 5 (*continued*)

Table 5 (*continued*)

Variables	Total (n=188)		Group A* (n=126)		Group B# (n=62)	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
FLT3-ITD						
Negative	1.0		1.0		1.0	
Positive	0.00 (0.00, Inf)	0.9953	0.00 (0.00, Inf)	0.9963	0.00 (0.00, Inf)	0.9972
Courses to CR1						
1	1.0		1.0		1.0	
2	2.36 (1.50, 3.71)	0.0002	2.17 (1.26, 3.74)	0.0055	2.87 (1.29, 6.42)	0.0101
≥3	2.44 (0.76, 7.85)	0.1359	2.42 (0.75, 7.84)	0.1404	-	
Allo-HSCT						
No	1.0		1.0		1.0	
Yes	0.68 (0.43, 1.06)	0.0915	0.74 (0.43, 1.25)	0.2565	0.55 (0.23, 1.29)	0.1702

*, defined as patients with t(8;21)-only or additional loss of Y chromosome; #, defined as patients with additional loss of X chromosome, del(9q), or complex karyotype; $, the median age. RFS, relapse-free survival; LDAC, low-dose cytarabine (<1 g/m^2); IDAC, intermediate-dose cytarabine (1–1.5 g/m^2); HiDAC, high-dose cytarabine (2–3 g/m^2); WBC, white blood cell count; HB, hemoglobin; PLT, platelets; BM, bone marrow; CR1, first complete remission; allo-HSCT, allogeneic hematopoietic stem cell transplantation; Inf, infinity.

univariate (*Table 3*) and multivariate analyses (*Table 4*). Compared with LDAC, IDAC was associated with a superior OS in univariate (IDAC *vs.* LDAC, HR =0.29, P=0.0076; HiDAC *vs.* LDAC, HR =0.15, P=0.0687, *Table 3*) and multivariate analysis (IDAC *vs.* LDAC, HR =0.21, P=0.0125; HiDAC *vs.* LDAC, HR =0.08, P=0.0457, *Table 4*), whereas there was no statistical difference shown between IDAC and HiDAC in both univariate (HR =0.52, P=0.5381, *Table 3*) and multivariate (HR =1.87, P=0.5764, *Table 4*) regression.

With respect to RFS, there was no significant difference among the 3 consolidation regimens in both group A (P=0.6080, *Figure 3C*) and group B (P=0.2591, *Figure 3D*). Univariate analysis (*Table 5*) and multivariate analysis (*Table 6*) also showed no difference in RFS between the 3 regimens in both group A and B.

Patients showed good survival with IDAC consolidation before allo-HSCT

Among the 188 enrolled patients, 130 (69.1%) received only chemotherapy as consolidation and 58 (30.9%) patients underwent allo-HSCT. To eliminate the potential influence of allo-HSCT on outcomes, we performed a stratified analysis by allo-HSCT status. Similar to the entire cohort, in group B, patients with IDAC showed superior OS compared with those with LDAC, whether in the allo-HSCT group (P=0.0075, *Figure 4A*) or chemotherapy-only group (P=0.0455, *Figure 4B*). Similarly, in group A, patients with IDAC had no association with better OS, whether they received allo-HSCT (P=0.8978, *Figure 4C*) or not (P=0.3775, *Figure 4D*). RFS was not statistically different among the 3 consolidation regimens in both group A and B, whether receiving allo-HSCT or not (*Figure 5*).

Interestingly, for patients who underwent allo-HSCT, the 5-year OS was up to 69.69% (group A, *Figure 4B*) and 100% (group B, *Figure 4D*) in patients receiving IDAC consolidation before allo-HSCT compared with LDAC patients who had a 5-year OS of 50% (group A, *Figure 4B*) and 40% (group B, *Figure 4D*).

Discussion

Ara-C is commonly used as consolidation therapy in t(8;21) AML. Our study demonstrated that there was no difference in OS and RFS between IDAC and HiDAC in t(8;21) AML. In other studies, with respect to OS, HiDAC has shown no better survival than IDAC in patients with favorable-risk disease (8,9,11,13,29), while there has been some controversy regarding RFS. Miyawaki *et al.* reported that patients receiving HiDAC treatment had superior disease-free survival (DFS) (29). Wu *et al.* showed better DFS for

Table 6 Multivariate analysis of RFS in the entire t(8;21) AML cohort (n=188), subcohort group A* (n=126), and subcohort B# (n=62)

Variables	Total (n=188)		Group A* (n=126)		Group B# (n=62)	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Consolidation						
LDAC	1.0		1.0		1.0	
IDAC	0.70 (0.41, 1.18)	0.1806	0.80 (0.40, 1.60)	0.5297	0.85 (0.32, 2.27)	0.7473
HiDAC	0.73 (0.37, 1.44)	0.3625	0.69 (0.29, 1.66)	0.4107	0.63 (0.16, 2.53)	0.5196
IDAC/HiDAC						
IDAC	1.0		1.0		1.0	
HiDAC	1.00 (0.55, 1.81)	0.9962	0.81 (0.40, 1.66)	0.5704	0.76 (0.20, 2.85)	0.6852
Sex						
Male	1.0		1.0		1.0	
Female	0.87 (0.56, 1.38)	0.5613	1.24 (0.73, 2.12)	0.4275	0.43 (0.18, 1.03)	0.0592
WBC ($\times10^9$/L)						
≤20	1.0		1.0		1.0	
>20	0.98 (0.60, 1.61)	0.9424	1.14 (0.64, 2.03)	0.6675	0.55 (0.14, 2.13)	0.3844
HB (g/L)						
≤100	1.0		1.0		1.0	
>100	1.32 (0.78, 2.24)	0.3046	1.22 (0.67, 2.23)	0.5143	2.14 (0.62, 7.43)	0.2301
PLT ($\times10^9$/L)						
≤20	1.0		1.0		1.0	
>20	0.65 (0.41, 1.02)	0.0600	0.87 (0.50, 1.50)	0.6089	0.28 (0.11, 0.71)	0.0073
Extramedullary						
Negative	1.0		1.0		1.0	
Positive	2.37 (1.19, 4.71)	0.0140	1.72 (0.71, 4.13)	0.2265	7.05 (1.81, 27.44)	0.0048
KIT mutation						
Negative	1.0		1.0		1.0	
Positive	1.36 (0.73, 2.52)	0.3277	1.84 (0.93, 3.62)	0.0796	0.60 (0.11, 3.43)	0.5684
WT1 overexpression						
Negative	1.0		1.0		1.0	
Positive	0.56 (0.30, 1.06)	0.0735	0.57 (0.27, 1.23)	0.1559	0.52 (0.13, 2.04)	0.3465
Courses to CR1						
1	1.0		1.0		1.0	
2	2.58 (1.61, 4.13)	<0.0001	2.81 (1.55, 5.11)	0.0007	2.94 (0.83, 10.39)	0.0933
≥3	1.72 (0.50, 5.99)	0.3921	1.88 (0.51, 6.90)	0.3403	1.0	
Allo-HSCT						
No	1.0		1.0		1.0	
Yes	0.76 (0.47, 1.23)	0.2653	0.67 (0.37, 1.19)	0.1714	0.83 (0.30, 2.28)	0.7113

*, defined as patients with t(8;21)-only or additional loss of Y chromosome; #, defined as patients with additional loss of X chromosome, del(9q), or complex karyotype. RFS, relapse-free survival; AML, acute myeloid leukemia; LDAC, low-dose cytarabine (<1 g/m^2); IDAC, intermediate-dose cytarabine (1–1.5 g/m^2); HiDAC, high-dose cytarabine (2–3 g/m^2); WBC, white blood cell count; HB, hemoglobin; PLT, platelets; CR1, first complete remission; allo-HSCT, allogeneic hematopoietic stem cell transplantation.

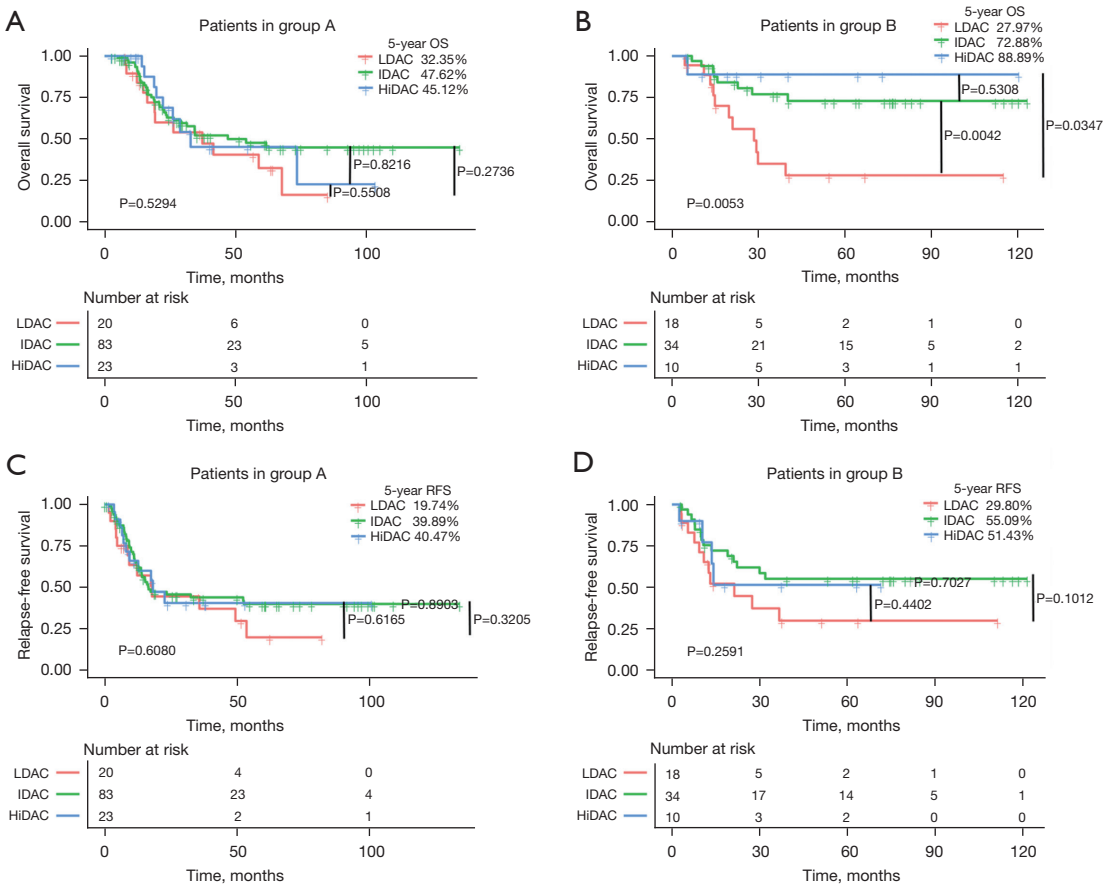

Figure 3 Prognostic impact of different doses of cytarabine in both cytogenetic layers. (A) OS in group A; (B) OS in group B; (C) RFS in group A; (D) RFS in group B. LDAC, low-dose cytarabine; IDAC, intermediate-dose cytarabine; HiDAC, high-dose cytarabine; OS, overall survival; RFS, relapse-free survival; group A, patients with t(8;21)-only or additional loss of Y chromosome; group B, patients with additional loss of X chromosome, del(9q), or complex karyotype.

HiDAC (8). Magina *et al.* found that the risk of recurrence was lower for HiDAC than IDAC (9). However, the study by Miyawaki *et al.* was designed to compare HiDAC and LDAC with other chemotherapy regimens, not directly with IDAC. The studies by Wu *et al.* and Magina *et al.* revealed the DFS/RFS benefit of HiDAC over IDAC in patients with favorable cytogenetics, not in an entire t(8;21) AML cohort.

In our study, compared with LDAC, patients with IDAC had better OS, which has also been found in other reports (11). Given the better survival of IDAC compared with LDAC and the fewer side effects of IDAC compared with HiDAC, the European LeukemiaNet (ELN) guidelines have recommended the IDAC regimen as acceptable consolidation therapy in t(8;21) AML since 2017 (26).

Although the IDAC regimen is the ELN guidelines' recommended post-remission therapy, there are heterogeneities among the different subtypes, making it possible to improve the therapeutic effect in t(8;21) AML patients. Patients with different karyotypes responded differently to IDAC consolidation in t(8;21) AML. In our study, we found that patients with additional -X, del(9q), or complex karyotype had better survival when receiving IDAC compared with LDAC as consolidation. However, in patients with t(8;21)-only or additional -Y cohort, there was no significant difference in OS or RFS between IDAC or LDAC. Considering the effect of HSCT, we performed a stratified analysis. When focusing on patients with t(8;21)-only or additional -Y, the IDAC regimen did not provide a superior prognosis compared with the LDAC regimen, while for patients with additional -X, del(9q), or complex karyotype, the IDAC regimen was associated with better

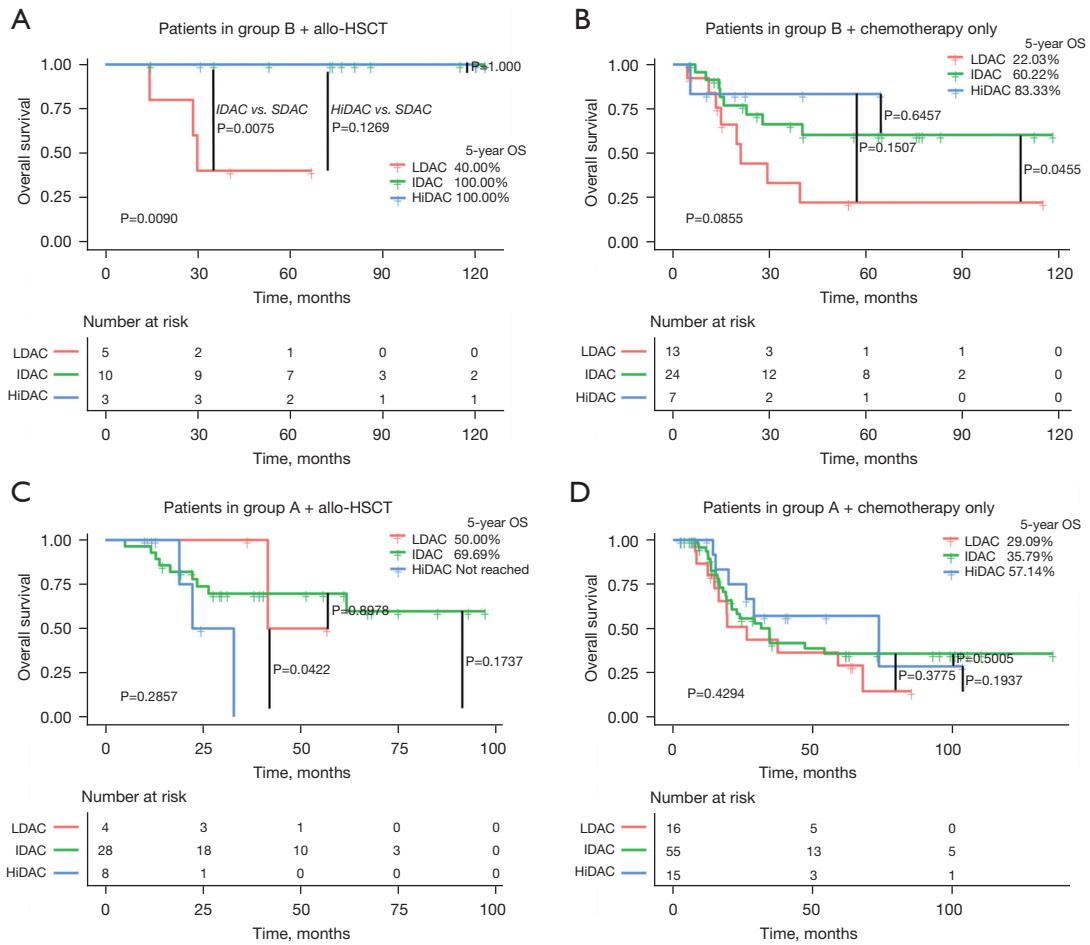

Figure 4 Estimated OS according to different doses of cytarabine in patients in group A or B, receiving allo-HSCT or not. (A) Patients in group B receiving allo-HSCT; (B) patients in group B receiving chemotherapy-only as consolidation; (C) patients in group A receiving allo-HSCT; (D) patients in group A receiving chemotherapy-only as consolidation. LDAC, low-dose cytarabine; IDAC, intermediate-dose Ara-C; HiDAC, high-dose cytarabine; OS, overall survival; group A, patients with t(8;21)-only or additional loss of Y chromosome; group B, patients with additional loss of X chromosome, del(9q), or complex karyotype; allo-HSCT, allogeneic hematopoietic stem cell transplantation.

survival, whether patients received HSCT or not. This suggested that the IDAC regimen might not be suitable for all patients with t(8;21) AML as consolidation therapy. Perhaps LDAC is sufficient for patients with t(8;21)-only or additional -Y.

Interestingly, for patients who received HSCT, IDAC consolidation before allo-HSCT might have contributed to higher OS compared with LDAC. For IDAC, the 5-year OS was up to 69.69% in group A and 100.00% in group B, while the 5-year OS was only 50.00% (group A) and 40.00% (group B) in patients with LDAC before HSCT. Some studies have reported that HSCT after a high dose of Ara-C showed lower risk of relapse (30,31), suggesting that allo-HSCT with prior IDAC consolidation might be a better therapeutic choice for patients with t(8;21) AML.

This study had some limitations. Although our retrospective study involved a relatively large multicenter cohort and had a follow-up period of over 10 years, randomized prospective studies will be required to confirm our results. Additionally, our study was limited to younger adult patients, and thus more research is needed for generalizing our conclusions to other settings. Patients receiving allo-HSCT with prior IDAC consolidation showed high 5-year OS. However, we did not compare allo-

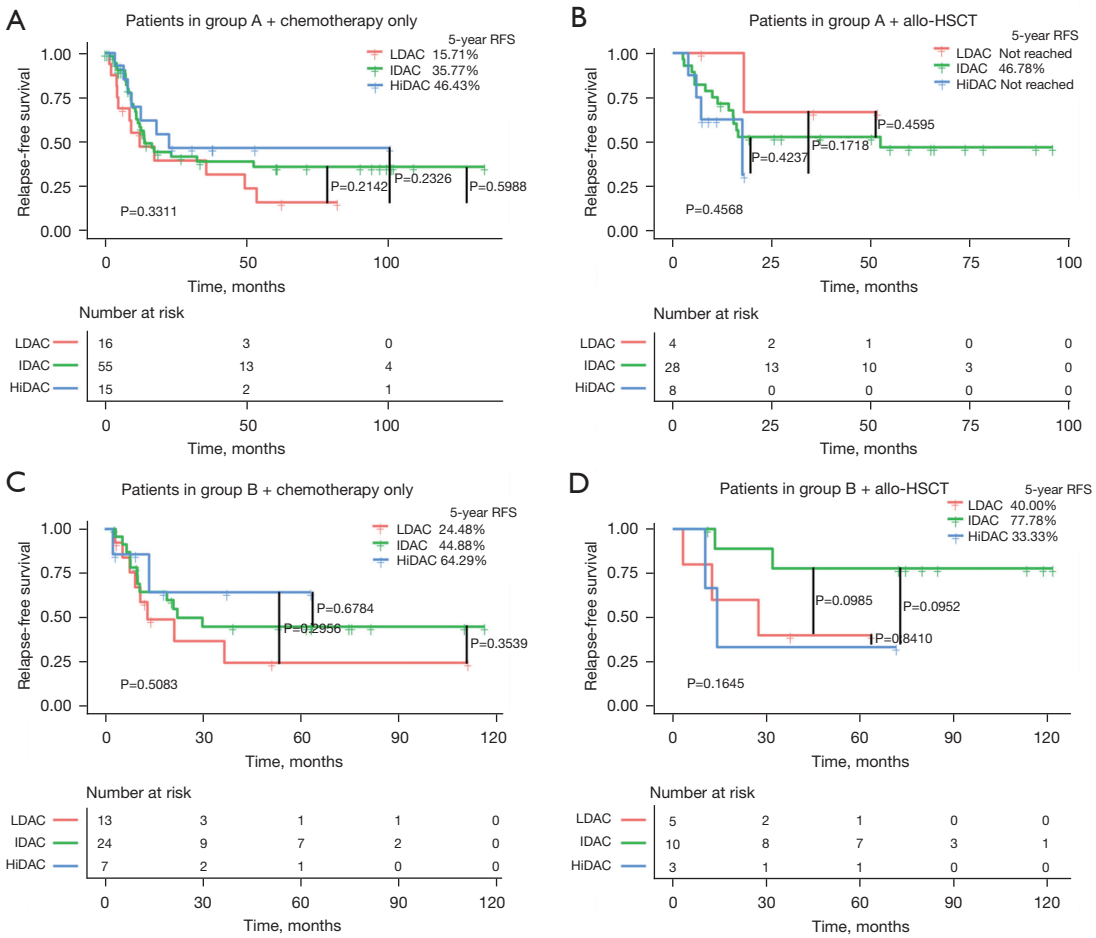

Figure 5 Estimated RFS according to different doses of cytarabine in patients in group A or B, receiving allo-HSCT or not. (A) Patients in group A receiving chemotherapy-only consolidation; (B) patients in group A receiving allo-HSCT; (C) patients in group B receiving chemotherapy-only consolidation; (D) patients in group B receiving allo-HSCT. LDAC, low-dose cytarabine; IDAC, intermediate-dose cytarabine; HiDAC, high-dose cytarabine; RFS, relapse-free survival; group A, patients with t(8;21)-only or additional loss of Y chromosome; group B, patients with additional loss of X chromosome, del(9q), or complex karyotype; allo-HSCT, allogeneic hematopoietic stem cell transplantation.

HSCT with chemotherapy-only groups, and we aim to explore this in our future research.

Conclusions

HiDAC resulted in no better therapeutic benefit than IDAC as consolidation therapy in t(8;21) AML. LDAC might be sufficient for patients with t(8;21)-only or additional -Y karyotype in t(8;21) AML. Future studies may help determine whether allo-HSCT with prior IDAC consolidation is a better therapeutic choice for t(8;21) AML patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.

amegroups.com/article/view/10.21037/atm-22-2965/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-2965/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2965/coif). 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Tianjin Medical University Cancer Institute and Hospital (No. bc2022154). All participating centers were informed and agreed the study. Individual consent for this retrospective analysis was waived.

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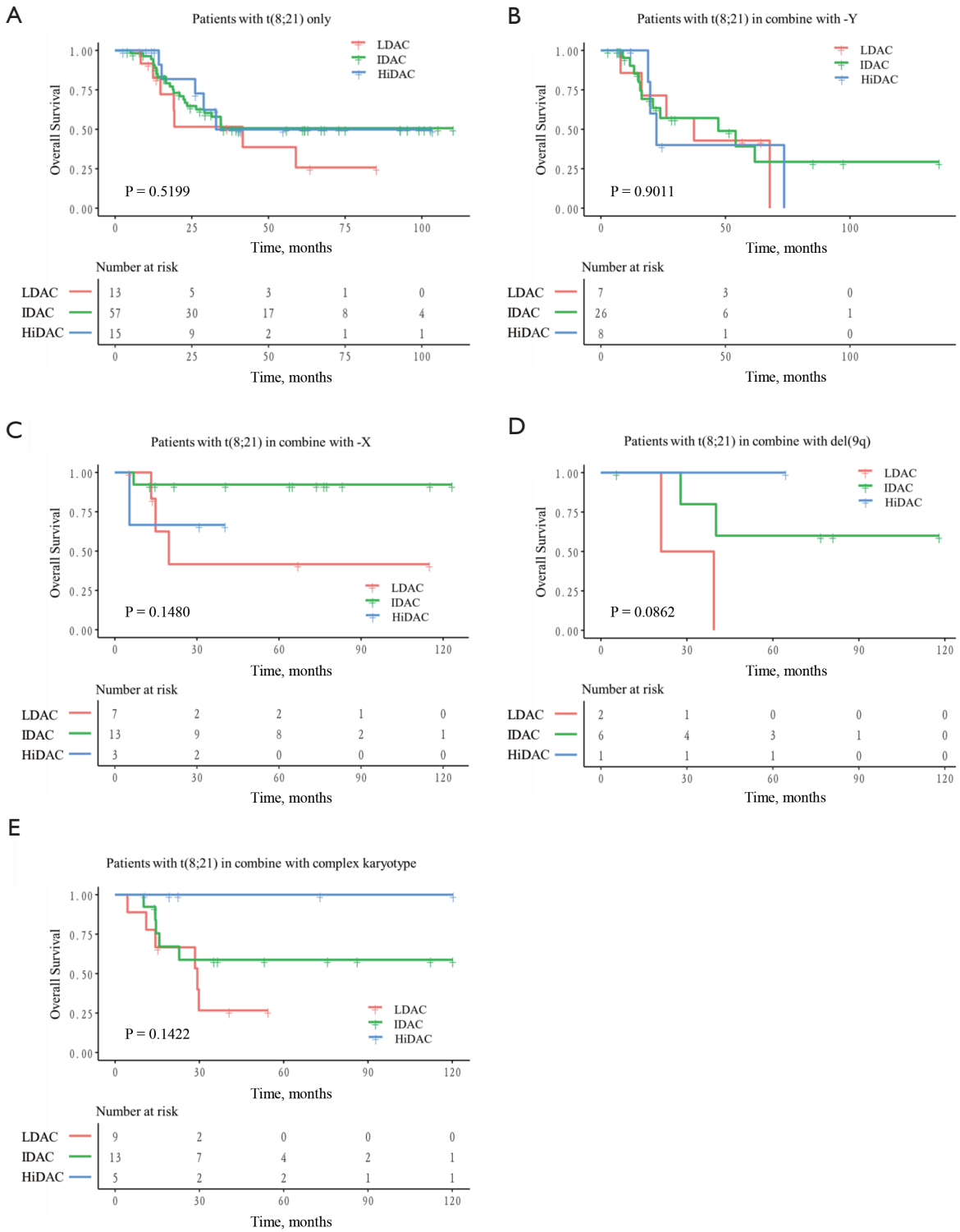

Figure S1 Estimated OS according to different doses of cytarabine consolidation therapy in patients with different cytogenetics. (A) Patients with t(8;21)-only karyotype; (B) patients with additional -Y karyotype; (C) patients with additional -X karyotype; (D) patients with additional del(9q) karyotype; (E) patients with complex karyotype. LDAC, low-dose cytarabine; IDAC, intermediate-dose Ara-C; HiDAC, high-dose cytarabine; OS, overall survival; -Y, loss of Y chromosome; -X, loss of X chromosome.

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