administered, the total dose of Ara-C was almost the same (72 g/m^2 vs 60 g/m^2). The Acute Leukemia French Association (ALFA) Group compared a timed-sequential consolidation consisting of ETP, MIT and Ara-C with a postremission chemotherapy including four cycles of HiDAC (3 g/m^2), and reported that there were no statistically significant differences between the two groups in the rates of event-free survival (EFS) and OS at 3 years.[15] The British Medical Research Council (MRC) also compared a conventional MRC schedule (MACE/MidAC) with two courses of HiDAC regimens (3 g/m^2 or 1.5 g/m^2), and reported that there were no significant differences in DFS and OS at 5 years.[16] On the contrary, the CALGB-8525 study[14] revealed that their HiDAC regimen was superior to the intermediate dose of Ara-C (400 mg/m^2 for 5 days) or to the conventional dose of Ara-C (100mg/m^2 for 5 days) regimens in DFS and OS, this plausibly comes from the lower dose-intensity of the intermediate or standard dose Ara-C regimens. In fact, the CALGB-9222 study[17] showed no difference in DFS and OS between the HiDAC group and the intensified sequential multi-agent chemotherapy group.

Cytogenetics is considered one of the most valuable prognostic determinants in adult AML[8,18]. In the present study, although in the intermediate risk group, the DFS and OS of both consolidation groups were almost identical, in the favorable risk group, the outcome of HiDAC group (n = 108) tended to be superior to that of Multiagent CT group (n = 110) in DFS (57% versus 39%) (P = 0.050) and OS (75% versus 66%) (P = 0.174) but not at statistically significant level, and, in the adverse risk group, the similar but statistically non-significant trend in DFS (33% versus 14%) and OS (39% versus 21%) was noted. Bloomfield et al.[19] reported that HiDAC regimen is the most effective to CBF leukemia. In their study, patients with CBF leukemia (n = 18) had a 78% chance of remaining CR at 5 years when treated with HiDAC regimen. However our study showed that DFS of CBF leukemia (n = 108) treated with HiDAC regimen was only 57% at 5 years.

There are two possible explanations of difference between our results and those reported by Bloomfield et al. One is that their superior results may come from a small number of patients (n = 18). In fact, the CALGB 9222 study[17]

including 28 patients with CBF leukemia demonstrated that the 5-year DFS and OS of CBF leukemia treated with HiDAC was 60% and 70%, respectively. These data are similar to our results. The other is that CBF leukemia reveals different sensitivity to HiDAC therapy. Some patients with CBF abnormality has KIT mutations which confer higher relapse risk on CBF AML.[20,21] CALGB reported that 29.5% of patients with inv(16) and 22% of patients with t(8;21) had KIT mutations and the cumulative incidence of relapse was higher for patients with mutated KIT than for those with wild type KIT.[20] The difference of mutation rates of KIT might result in the difference in DFS. Unfortunately, in our present study, KIT mutations were not prospectively evaluated. However, high mutation rate of KIT is reported among Asian patients with t(8;21) from Japan (37.8%)[22] and China (48.1%)[23]. Consequently, JALSG is prospectively evaluating KIT mutation and its impact on the outcome in patients with CBF leukemia treated with repetitive HiDAC therapy. In the adverse cytogenetic risk group, the outcome of the HiDAC group also tends to be better than that of the Multiagent CT group, but the difference is not statistically significant. Small number of this

cohort may explain the statistical insignificance. Nevertheless, HiDAC therapy may be recommended to this group if patients have no HLA-matched donor.

Recently IDR is frequently included into induction regimen for AML because of its better effectiveness comparing with DNR.[24-26] Actually a meta-analysis of randomized trials showed that the use of IDR instead of DNR results in s high CR rate.[27] However, German group reported that the advantage of IDR in response rate may be lost during HiDAC consolidation therapy due to increased toxicity in the IDR group.[28] However, our current study demonstrated that, among the HiDAC group, there is no difference in DFS and OS between patients receiving IDR or DNR in induction phase. In our study, although one or two courses of the IDR regimen were given before the HiDAC consolidation, only 19% of patients required two courses to obtain CR. In contrast, German group gave two courses of IDR induction regimen before the HiDAC consolidation. Thus, severe adverse events during HiDAC therapy likely depend on the total dose of prior IDR. Nevertheless, the HiDAC regimen could be given safely in our patients who had received IDR as induction therapy.

We conclude that post-remission consolidation regimen should be selected on the basis of such prognostic factors as cytogenetics. Although several types of HiDAC regimen have been widely adopted as the optimal post-remission therapy, the conventional Multiagent CT may be recommendable for the intermediate or adverse cytogenetic risk groups. However, our HiDAC regimen should be recommended to the favorable cytogenetic risk group.

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Authorship

Contribution: S.M. designed and performed research, interpreted data, and wrote the manuscript; S.O. designed and performed research, and collected and analyzed data, and participated in writing manuscript; S.F., H.K., K.S., N.U., T.S., K.M., C.N., Y.M., M.M., T.N., T.Y., A.F., M.T., F.Y., Y.K., N.A., H.S., H.H., S.H., K.O., and T.N. performed research; R.O. interpreted data, and participated in writing manuscript.

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Table 1. Clinical Characteristics of Randomized Patients

	HiDAC (n = 389)	Multiagent CT (n = 392)	*P* value
Age (year)	46 (15-64)	47 (15-64)	0.697
WBC ($x10^9$/L)	15.6 (0.1-382)	14.9 (0.2-260)	0.323
Karyotype			
Favorable	108	110	0.210
Intermediate	242	256	
Adverse	27	14	
Unknown	12	12	
Induction			
IDR	196	196	0.914
DNR	193	196	
Induction 1cycle (%)	81.0	81.4	0.886

Number indicates the median, and parentheses the range

Table 2. Factors to predict unfavorable prognostic features for DFS and OS by multivariate analysis

a. DFS

variables		hazard ratio	*P* value
Initial WBC Count	>= 20 x 10^9 /L	1.49	<.0001
No of Induction therapies	2 courses	1.50	0.0006
Age	> 50 y.o.	1.33	0.0028
Consolidation therapy	Multiagent CT	1.04	0.7128

b. OS

variables		hazard ratio	*P* value
Age	> 50 y.o.	2.00	<.0001
No of Induction therapies	2 courses	1.58	0.0033
Initial WBC Count	>= 20 x 10^9 /L	1.41	0.0070
MPO-positive blast	< 50 %	1.42	0.0149
Consolidation therapy	Multiagent CT	0.96	0.7768

Table 3. Tolerance of Consolidation

	% receiving the full courses	
	HiDAC	Multiagent CT
All patients	72.5	70.2
Patients ≤ 50yr of age	71.9	69.0
Patients > 50yr of age	73.4	71.9
Reason for not receiving the full courses (No. of Pat.)		
Relapse	18	31
Death	10	8
SCT in 1st CR	31	42
Adverse event*	27	13
Patient refusal	11	5
Unknown	10	19

*$P < 0.05$

Table 4. Intensity of Consolidation

	HiDAC	Multiagent CT	*P* value
After 1st Consolidation			
Lowest WBC (x 10^9/L)	0.17	0.40	< 0.0001
Days WBC < 1.0 x 10^9/L	13	12	0.0005
	(0-40)	(0-36)	
After 2nd Consolidation			
Lowest WBC (x 10^9/L)	0.10	0.40	< 0.0001
Days WBC < 1.0 x 10^9/L	14	13	0.0007
	(0-34)	(0-241)	
After 3rd Consolidation			
Lowest WBC (x 10^9/L)	0.10	0.40	<0.0001
Days WBC < 1.0 x 10^9/L	14	11.5	<0.0001
	(0-38)	(0-28)	
After 4th Consolidation			
Lowest WBC (x 10^9/L)		0.40	
Days WBC < 1.0 x 10^9/L		12	
		(0-34)	

Number indicates the median, and parentheses the range

Table 5. Adverse Events (CTC grades 3 and 4) During Consolidation Therapy

	HiDAC	Multiagent CT	*P*
	%	%	Value
Documented Infection	20.9	14.5	< 0.001
Febrile Neutropenia	66.5	66.4	0.311
Bleeding	0.8	0.7	0.601
Early Death*	0.9	0.6	0.389

Early Death*: death within 30 days after consolidation chemotherapy

Figure Legends

Figure 1: CONSORT diagram

IDR, idarubicin; DNR, daunorubicin; Ara-C, cytarabine, HiDAC, high-dose cytarabine.

Figure 2: Disease-free survival and overall survival according to treatment arm.

a: Disease-free survival of CR patients. Predicted 5-year DFS was 43% for the HiDAC group (n = 389) (red line) and 39% for the Multiagent CT group (n = 392) (blue line) ($P = 0.724$).

b: Overall survival of CR patients. Predicted 5-year OS was 58% for the HiDAC

group (n = 389) (red line) and 56% for the Multiagent CT group (n = 392) (blue line) ($P = 0.954$).

Figure 3: Disease-free survival and overall survival according to treatment arm, after censoring the observation in transplanted patients.

Predicted 5-year DFS was 41% for the HiDAC group (n = 389) (red line) and 36% for the Multiagent CT group (n = 392) (blue line) ($P = 0.608$).

Figure 4: Cumulative incidence of relapse and treatment related mortality in CR by treatment arm.

a: The incidence of relapse and mortality were 49% and 8% for the HiDAC group (solid line), and 56% and 5% for the Multiagent CT group (dotted line) ($P = 0.324$, $P = 0.172$).

b: After censoring the observation in transplanted patients, the incidence of relapse and mortality were 55% and 4% for the HiDAC group (solid line), and 61% and 3% for the Multiagent CT group (dotted line) ($P = 0.402$, $P = 0.409$),

Figure 5: Disease-free survival and overall survival by treatment arm for the favorable cytogenetic risk group.

a: Predicted 5-year DFS was 57% for the HiDAC group (n = 108) (red line) and 39% for the Multiagent CT group (n = 110) (blue line) ($P = 0.050$).

b: Predicted 5-year OS was 75% for the HiDAC group (n = 108) (red line) and 66% for the Multiagent CT group (n = 110) (blue line) ($P = 0.174$).

Figure 6: Disease-free survival and overall survival by treatment arm for the intermediate cytogenetic risk group.

a: Predicted 5-year DFS was 38% for the HiDAC group (n = 242) (red line) and 39% for the Multiagent CT group (n = 256) (blue line) ($P = 0.403$).

b: Predicted 5-year OS was 53% for the HiDAC group (n = 242) (red line) and 54% for the Multiagent CT group (n = 256) (blue line) ($P = 0.482$).

Figure 7: Disease-free survival and overall survival by treatment arm for the