demonstrate 10% superiority in 5-year DFS for the HiDAC arm (40% vs 30%). OS was defined as the time interval from the date of diagnosis to the date of death. DFS for patients who had achieved CR was defined as the time interval from the date of CR to the date of the first event (either relapse or death). Patients who underwent allo-SCT were not censored. The Kaplan-Meier method was used to estimate probabilities of DFS and OS. For comparison of DFS and OS, the log-rank test was used for univariate analysis and the proportional hazard model of Cox for multivariate analysis. Cumulative incidence of relapse and treatment related mortality were estimated according to the competing risk method and were evaluated with Gray's test. The Wilcoxon rank-sum test was used for continuous data such as age and WBC count, while the chi-square test was used for ordinal data such as risk group and frequency of allo-SCT. Statistical analyses were conducted using the JMP program (SAS Institute Inc., Cary, NC) and R software (www.r-project.org).

Results

Response to Induction Therapy

Of 1,064 patients registered, 1,057 patients were evaluable. Seven patients (misdiagnosis: one, infectious complication: one, without therapy: one, and withdrawal of consent: 4) were excluded. Median age was 47 years (range, 15 to 64). Cytogenetic studies were performed in 99.2% of registered patients and the results were available in 97%. Of 1,057 evaluable patients, 823 (78%) achieved CR (662 of them after the first induction course). CR rate in the IDR and DNR arms was similar (78.2% versus 77.5%). Percentage of patients who reached CR after the first induction course was also similar (64.1% versus 61.1%, $P = 0.321$). Day to achieve CR was longer in the IDR arm than the DNR arm (33.8 versus 32.4 days, $P = 0.038$). The detailed result of induction phase of this study is reported in a separate paper.[10]

Post-remission Randomization

Of 823 patients who achieved CR, 42 did not undergo the second

randomization for a variety of reasons, which included residual toxicity from induction therapy (12), allo-SCT (8), death (1), refusal (1) and unknown (20). Remaining 781 patients were randomly assigned to receive either the HiDAC regimen (389) or the Multiagent CT regimen (392) (Fig. 1). Clinical characteristics of two treatment groups were well balanced in age, initial WBC count, cytogenetic risk, induction arm, and induction cycle (Table 1).

Disease-free Survival and Overall Survival

The median follow-up period of living patients was 48 months (range, 5-78 months). Five-year DFS was 43% for the HiDAC group and 39% for the Multiagent CT group (P = 0.724) (Fig. 2-a). Five-year OS was 58% for the HiDAC group and 56% for the Multiagent CT group (P = 0.954) (Fig. 2-b). After censoring the observation on the date of SCT in transplanted patients, 5-year DFS was 41% for the HiDAC group and 36% for the Multiagent CT group (P = 0.608) (Fig. 3).

The cumulative incidence of relapse and treatment-related mortality during CR

were 49% and 8% for the HiDAC group and 56% and 5% for the Multiagent CT group (P = 0.294, P = 0.172), respectively (Fig. 4-a). After censoring the observation in transplanted patients, those were 55% and 4% for the HiDAC group and 61% and 3% for the Multiagent CT group (P = 0.402, P = 0.409), respectively (Fig. 4-b).

In patients with the favorable cytogenetics, i.e. core-binding factor (CBF) leukemia with t(8;21) or inv(16), 5-year DFS was 57% in the HiDAC group and 39% in the Multiagent CT group (P = 0.050) (Fig. 5-a), and 5-year OS was 75% and 66%, respectively (P = 0.174) (Fig. 5-b).

In patients with the intermediate cytogenetics, 5-year DFS was 38% in the HiDAC group and 39% in the Multiagent CT group (P = 0.403) (Fig. 6-a), and 5-year OS was 53% and 54%, respectively (P = 0.482) (Fig. 6-b). In patients with the adverse cytogenetics, 5-year DFS was 33% in the HiDAC group and 14% in the Multiagent CT group (P = 0.364) (Fig. 7-a), and 5-year OS was 39% and 21%, respectively (P = 0.379) (Fig. 7-b). Among younger patients of age 50 years or less, 5-year DFS was 45% in the HiDAC group and 46% in the

Multiagent CT group ($P = 0.590$), and 5-year OS was 62% and 66%, respectively ($P = 0.228$). Among the older patients (> 50 years), 5-year DFS was 40% in the HiDAC group and 28% in the Multiagent CT group ($P = 0.230$), and 5-year OS was 51% and 40%, respectively ($P = 0.159$). In patients treated with the IDR regimen at induction, 5-year DFS was 42% in the HiDAC group and 41% in the Multiagent CT group ($P = 0.641$), and 5-year OS was 58% and 57%, respectively ($P = 0.790$). In patients treated with the DNR regimen at induction, 5-year DFS was 44% in the HiDAC group and 37% in the Multiagent CT group ($P = 0.339$), and 5-year OS was 58% and 56%, respectively ($P = 0.713$). There was no relationship between the duration of myelosuppression and DFS or OS.

Significant unfavorable prognostic features for DFS by the Cox proportional hazard model were WBC more than 20 x 10^9/L, the number of induction therapies and age of more than 50 years, and for OS, age of more than 50 years, the number of induction therapies, WBC more than 20 x 10^9/L and MPO-positive blast less than 50%. Induction therapy, consolidation therapy and cytogenetic risk group, were not an independent prognostic factor for DFS or

OS by this multivariate analysis (Table 2).

Tolerance and Toxicity of Post-remission therapy

All courses of consolidation were administered to 72.5% of patients in the HiDAC group and 70.2 % in the Multiagent CT group (Table 3). In the HiDAC group, 110 patients (28%) did not receive all 3 courses. The reasons included relapse (18), death in CR (10), allo-SCT (34), adverse events (27), patient's refusal (11) and unknown (10). In the Multiagent CT group, 118 patients (30%) did not receive all 4 courses. The reasons included relapse (31), death in CR (8), allo-SCT (42), adverse events (13), patient's refusal (5) and unknown (19). The most common reason was allo-SCT in both groups. Of 125 patients received SCT in 1st CR, 49 (25 in HiDAC and 24 in Multiagent CT) received SCT after completion of full courses of consolidation therapy. The second common reason was adverse events in the HiDAC group, and relapse in the Multiagent CT group. The patients older than 50 years could tolerate both regimens. Table 4 shows a comparison of both groups regarding the nadir of WBC count, and the number of days of WBC $< 1.0 \times 10^9$/L. After each course of

consolidation, the nadir of WBC count was significantly lower ($P < 0.0001$) and the day of WBC < 1.0 x 10^9/L was significantly longer in the HiDAC group ($P < 0.001$). During each course of consolidation, the frequency and the number of days of G-CSF administration were significantly higher in the HiDAC group. Table 5 shows toxic adverse events excluding hematological side effects. The frequency of documented infections was significantly higher in the HiDAC group ($P < 0.001$). The subset analysis showed the high incidence of documented infection in HiDAC regimen only in intermediate cytogenetic risk group ($P < 0.001$).

Discussion

To determine the best post remission therapy, there have been several prospective randomized studies comparing chemotherapy with SCT. Although there is some limitation in SCT such as patient's age and availability of HLA-identical donors, most randomized studies demonstrate that SCT, the most intensive post-remission modality, provides superior or at least

non-inferior prognosis in high or intermediate risk adult AML.[11-13]

As for post-remission chemotherapy, HiDAC therapy is generally used in U.S.A and other countries after the landmark CALGB-8525 study.[14] In Japan, however, since HiDAC therapy was not approved by our national medical insurance system until 2001, combination chemotherapy using non-cross resistant agents was commonly used in previous studies for adult AML. Therefore, in the current study, we compared conventional Multiagent CT with HiDAC therapy.

Our study demonstrated that there is no difference in DFS and OS between the Multiagent CT regimen and the HiDAC regimen. The HiDAC regimen, however, was accompanied with more frequent infectious events due to severer and longer-lasting neutropenia. In the CALGB-8525 study,[14] patients randomized to 4 cycle of HiDAC regimen were administered 3 g/m^2 of Ara-C by 3-hour infusion, twice daily on days 1, 3 and 5, and our patients randomized to 3 cycle of HiDAC regimen were given 2 g/m^2 of Ara-C by 3-hour infusion, twice daily for 5 days. Although there were some differences in schedule and dose

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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