



Oral Maintenance Chemotherapy with 6-Mercaptopurine and Methotrexate in Patients with Acute Myeloid Leukemia Ineligible for Transplantation

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For decades, maintenance chemotherapy has failed to improve the cure rate or prolong the survival of patients with acute myeloid leukemia (AML), other than those with acute promyelocytic leukemia. Immediately after the first complete remission following consolidation therapy was obtained, oral maintenance chemotherapy (daily 6-mercaptopurine and weekly methotrexate) was given and continued for two years in transplant-ineligible AML patients. Leukemia-free survival (LFS) and overall survival (OS) were studied and compared between these patients and the historical control group who did not receive maintenance therapy. Consecutive 52 transplant-ineligible AML patients were analyzed. Among these patients, 27 received oral maintenance chemotherapy. No significant difference was found in the patients' characteristics between the maintenance and the control groups. The median OS was 43 (95% CI, 19-67) and 19 (95% CI, 8-30) months in the maintenance and the control groups, respectively ($P = 0.202$). In the multivariate analysis, the presence of maintenance therapy was an independent prognostic factor for better OS ($P = 0.021$) and LFS ($P = 0.024$). Clinical benefit from maintenance chemotherapy was remarkable in older patients (≥ 60 yr) ($P = 0.035$), those with intermediate or unfavorable cytogenetics ($P = 0.006$), those with initial low blast count in peripheral blood ($P = 0.044$), and those receiving less than two cycles of consolidation therapy ($P = 0.017$). Maintenance oral chemotherapy as a post-remission therapy can prolong the survival of patients with AML who are not eligible for transplantation, particularly older patients, those with intermediate or unfavorable cytogenetics, those with initial low blast count, and those receiving less than two cycles of consolidation therapy.

Keywords: Maintenance; Leukemia; Myeloid; Acute

INTRODUCTION

Acute myeloid leukemia (AML) is the most common type of leukemia, and it has the lowest survival rate of all leukemia types in adults (1). Although attaining complete remission (CR) is the important goal of initial therapy in AML, the median disease free survival of patients who received the induction therapy only without post-remission therapy is four to eight months (2, 3). In the past two decades, little has changed in induction chemotherapy (4). However, improved understanding of the AML biology with modern cytogenetics and molecular testing has led to the customization of post-remission therapy based on relapse risk-stratification (5, 6). Hematopoietic stem cell transplantation (HSCT) has been considered a potentially curative therapy for AML with intermediate and adverse cytogenetics (7). However, several factors, such as old age, absence of a matched donor, and comorbidities, enable only about one-third of patients

to be eligible for HSCT (8). The remaining patients who cannot receive HSCT should be followed up until disease progression after two to four courses of high-dose cytarabine-based chemotherapy and more than half of these patients eventually relapse (9). For decades, although several trials with different strategies of maintenance therapy have been conducted to reduce the relapse of disease in patients, these trials have failed to show the improvement of outcomes (10-13). Consequentially, maintenance chemotherapy is not a standard therapy for AML except for acute promyelocytic leukemia (APL).

Nonetheless, reducing the relapse rate and the prolongation of the relapse free interval by minimizing the residual disease and preventing the regrowth of dormant leukemic stem cells through the prolonged exposure to maintenance chemotherapy remain attractive (14). The maintenance therapy with low dose cytotoxic agents 6-mercaptopurine (6MP) and methotrexate (MTX) has been clinically proven beneficial to ALL (15) and

APL (16). However, no study has been conducted yet to prove the clinical benefit of this therapy in AML. In this study, we retrospectively analyzed the clinical outcomes of AML patients who received oral maintenance therapy with 6MP and MTX after remission induction and consolidation therapy.

MATERIALS AND METHODS

Patients

From a single institute, 52 AML patients including those who were ineligible for HSCT (Age \geq 65, absence of a matched donor and significant comorbidities) received at least one cycle of consolidation therapy in the first complete remission (CR1) were analyzed. Among these patients, 27 received maintenance chemotherapy and 25 did not.

Treatment

Patients received 6MP (50 mg/day, p.o.) and MTX (10 mg/week, p.o.) for two years or until disease progression. The historical control group had completed remission induction and at least one cycle of consolidation therapy. Then, the group received no specific anti-leukemic treatment.

Definitions and statistical analysis

Initial diagnosis and leukemia subtypes were recorded using the French-American-British (FAB) classification system (17). Cytogenetics were classified into 3 risk groups: favorable, t(8;21), inv(16); intermediate, normal karyotype or other numerical or

structural abnormalities; unfavorable, 11q23 rearrangement, -5, del(5q), -7, del(7q), inv(3)/t(3;3)/ins(3;3). Leukemia-free survival (LFS) was calculated from the date of diagnosis to the last follow-up or first event (failure to achieve remission, demonstration of resistant leukemia, or relapse). Overall survival (OS) was defined as the time from diagnosis to death from any cause. The characteristics of the two groups were compared by the chi-square test or Fischer's exact test for categorical data and the Mann-Whitney U-test for continuous variables. LFS and OS were estimated by the Kaplan-Meier method and compared by the Log Rank and Breslow method. The Cox proportional hazard model was used in the multivariate analysis of prognostic factors. *P* values lower than 0.05 were considered statistically significant. Statistical analysis was performed using SPSS version 13.0 (IBM, Armonk, NY, USA).

Ethics statement

The study (AJIRB-MED-MDB-14-258) was approved by the Ajou University Hospital institutional review board. The board waived written informed consent.

RESULTS

Patient and disease characteristics

The patient and disease characteristics are given in Table 1. No significant difference was found in the baseline patient and disease characteristics between the maintenance and the historical control groups.

Table 1. Patients characteristics

Parameters	Total	Maintenance	Control	<i>P</i> value
Number of patients, N (%)	52 (100)	27 (51.9)	25 (48.1)	
Median age, yr (range)	53 (18-74)	55 (21-69)	48 (18-74)	0.126
Age \geq 60, N, (%)	17 (32.7)	11 (40.7)	6 (24.0)	0.199
Gender (male/female), N (%)	24:28 (46.2:53.8)	13:14 (48.1:51.9)	11:14 (46.4:53.6)	0.788
ECOG PS $<$ 2, N (%)	50 (96.2)	25 (92.6)	25 (100)	0.360
FAB subtype, N (%)				0.145
M0-M2	30 (57.7)	14 (51.9)	16 (64.0)	
M4-M5	20 (38.5)	13 (48.1)	7 (28.0)	
M6-M7	2 (3.8)	0 (0.0)	2 (8.0)	
MDS/therapy related AML, N (%)	8 (15.4)	4 (14.8)	4 (16)	0.906
Cytogenetic risk group, N (%)				0.139
Favorable	17 (32.7)	7 (25.9)	10 (40.0)	
Intermediate	33 (63.5)	20 (74.1)	13 (52.0)	
Unfavorable	2 (3.8)	0 (0.0)	2 (8.0)	
LDH (U/L), median (range)	426 (123-4027)	436 (156-2014)	419 (123-4027)	0.653
Baseline CBC				0.978
Hb, median (range)	7.4 (2.3-10.7)	7.5 (3.0-10.7)	6.9 (2.3-10.7)	0.327
Plt, median (range)	48.5 (6-353)	57 (11-316)	40.0 (6-353)	0.742
WBC, median (range)	13.4 (0.7-358)	14.1 (0.7-97.5)	10.4 (1.9-358)	
Initial median				0.527
PB Blasts (% , range)	35.5 (0-89)	31 (0-84)	45.0 (0-89)	
Initial median				0.756
BM Blasts (% , range)	65.2 (20-98)	64.8 (20-98)	65.5 (21.1-95)	

ECOG PS, Eastern Cooperative Oncology Group (ECOG) performance status; FAB, French-American-British; MDS, myelodysplastic syndrome; LDH, lactate dehydrogenase; CBC, complete blood count; Hb, hemoglobin; Plt, platelet; WBC, white blood cell; PB, peripheral blood; BM, bone marrow.

Treatment results

The treatment characteristics for induction, number of consolidation therapy, and cause of death are presented in Table 2. Almost all patients (96.4%) received remission induction chemotherapy with idarubicin and cytarabine. More than one-half of the patients received more than two cycles of consolidation chemotherapy. Relapse was observed in 27 patients (51.9%) who achieved CR after induction treatment. Median LFS and OS were 28 months (95% confidence interval [CI], 1-44 months) and 29 months (95% CI, 10-48 months), respectively. Disease progression (54.5%) was the main cause of death, followed by infection (34.5%). The rate of achieving CR and the number of consolidation were not statistically different between the two groups.

OS, LFS, and prognostic factors

The median OS was 43 months and 19 months in the maintenance group and the historical control group, respectively (Log

Rank [$P = 0.202$], Breslow [$P = 0.044$], Fig. 1A). The median LFS was 31 months and 12 months in the maintenance group and historical control group, respectively (Log Rank [$P = 0.261$], Breslow [$P = 0.090$], Fig. 1B). In the multivariate analysis (Table 3), older age was an independent poor prognostic factor for OS ($P = 0.020$) and LFS ($P = 0.028$). Maintenance therapy was independently associated with favorable OS ($P = 0.021$) and LFS ($P = 0.024$). Higher baseline WBC count was associated with shorter LFS ($P = 0.033$).

Subgroup analysis

Subgroup analysis was performed using a univariate Cox proportional hazard model to evaluate the effects of maintenance treatment on OS and LFS (Table 4). All hazard ratios were made for patients who received maintenance treatment in comparison with those who did not. The OS (50 months vs. 16 months, $P = 0.004$, Fig. 2A) and LFS (not reached vs. 10 months, $P = 0.011$) were significantly prolonged with oral maintenance therapy when the cytogenetic study showed intermediate or unfavorable risk. Furthermore, clinical benefit from maintenance chemotherapy (OS and LFS) was documented for patients aged ≥ 60 yr (total: 17 patients, maintenance group: 11 patients, control group: 6 patients), ($P = 0.035$, Fig. 2B and $P = 0.019$), those with low peripheral blood (PB) blast count at diagnosis ($P = 0.044$, Fig. 2C and $P = 0.022$), and those who received less than two cycles of consolidation chemotherapy ($P = 0.017$, Fig. 2D and $P = 0.016$).

Table 2. Characteristics in treatment and results for induction and consolidation chemotherapy

Parameters	Total	Maintenance	Control	<i>P</i> value
Remission induction chemotherapy	52	27	25	0.491
Idarubicin/Ara-C	51 (98.1)	27 (100.0)	24 (96.0)	
Daunorubicin/Ara-C	1 (1.9%)	0 (0.0)	1 (4.0)	
CR after 1st remission induction chemotherapy	46 (88.5)	24 (88.9)	22 (88.0)	0.920
Number of consolidation therapy				0.213
1	13 (25.0)	7 (25.9)	6 (24.0)	
2	28 (53.8)	17 (63.0)	11 (44.0)	
3	11 (21.2)	3 (11.1)	8 (32.0)	
Cause of death				0.851
Disease progression	21 (72.4)	12 (75.0)	9 (69.2)	
Infection	3 (10.3)	2 (12.5)	1 (7.7)	
Hemorrhage	2 (6.9)	1 (6.3)	1 (7.7)	
Others	3 (10.3)	1 (6.3)	2 (15.4)	

Ara-C, cytosine arabinoside; CR, complete remission.

DISCUSSION

Despite intensive consolidation after achieving CR in patients with AML, less than one-third of the patients were cured, mainly because of the high incidence of relapse (18). Although sev-

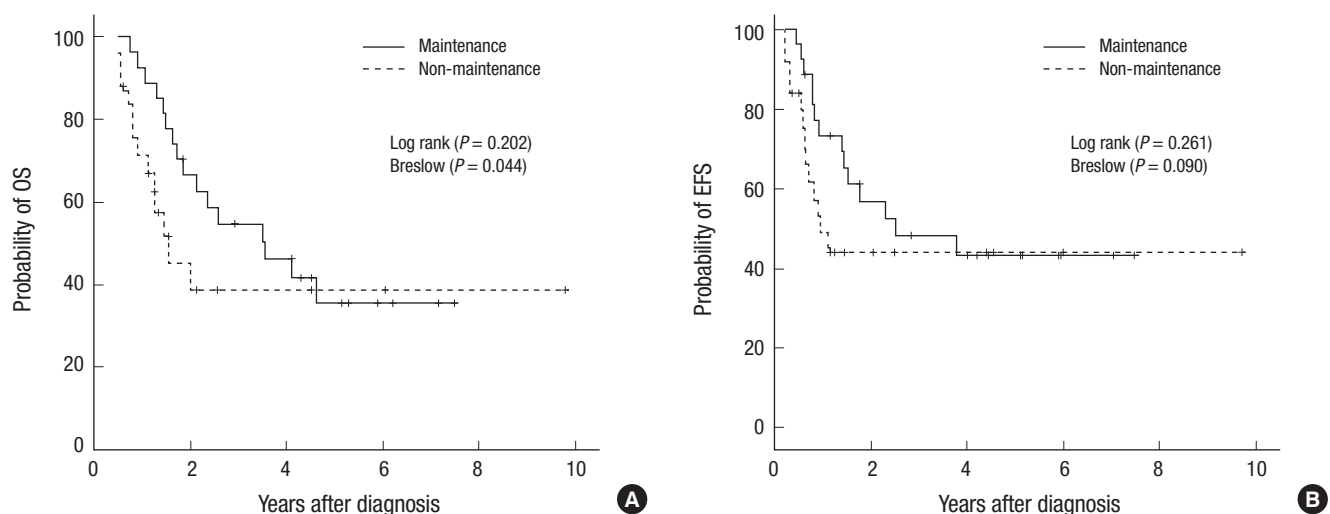


Fig. 1. Survival by the presence or absence of maintenance therapy. (A) Overall survival (OS). (B) Leukemia-free survival (LFS).

Table 3. Multivariate analysis of OS and LFS

Variables	OS			LFS		
	HR	95% CI	P value	HR	95% CI	P value
Age (10-yr increase)	1.50	1.07-2.10	0.020	1.49	1.04-2.12	0.028
Gender (Male vs. female)	0.80	0.31-2.07	NS			
ECOG PS (0/1 vs. 2/3/4)	0.35	0.04-2.87	NS	0.30	0.04-2.42	NS
Chromosome (Favorable vs. Intermediate/unfavorable)	0.94	0.32-2.77	NS	1.01	0.31-3.35	NS
De novo AML vs. Secondary AML	1.417	0.46-4.35	NS	0.70	0.20-2.45	NS
FAB (M1/M2 v M0, M4, M5, M6)	0.56	0.23-1.35	NS	0.64	0.27-1.52	NS
WBC, $\times 10^9/L$ (10-fold value)	2.09	0.99-4.40	NS	2.33	1.07-5.09	NS
Hemoglobin (g/L)	1.00	0.79-1.27	NS	0.90	0.71-1.16	NS
Platelet, $\times 10^9/L$	1.27	0.51-3.14	NS	1.41	0.53-3.75	NS
PB blast count (%)	1.00	0.98-1.02	NS	1.01	0.99-1.03	NS
BM blast count (%)	1.01	0.99-1.03	NS	1.01	0.99-1.03	NS
LDH, U/L (10-fold value)	0.99	0.30-3.29	NS	1.25	0.39-4.02	NS
N of consolidation Tx. (0,1 vs. 2,3)	0.65	0.26-1.59	NS	0.43	0.17-1.07	NS
Non-maintenance vs. Maintenance	0.33	0.13-0.84	0.021	0.33	0.13-0.87	0.024

OS, overall survival; LFS, leukemia free survival; HR, Hazard ratio; CI, confidence interval; NS, not significant; ECOG PS, Eastern Cooperative Oncology Group (ECOG) performance status; AML, acute myeloid leukemia; FAB, French-American-British; LDH, lactate dehydrogenase All candidate prognostic factors were included in the Cox regression model without selection of variables.

Table 4. Subgroup analysis of OS and LFS

Parameters	OS			LFS		
	HR	95% CI	P value	HR	95% CI	P value
Age < 60	0.86	0.34-2.22	NS	0.97	0.38-2.56	NS
Age \geq 60	0.23	0.06-0.90	0.035	0.17	0.04-0.74	0.019
Favorable cytogenetics	2.49	0.62-10.07	NS	2.48	0.59-10.39	NS
Intermediate/Unfavorable cytogenetics	0.27	0.11-0.69	0.006	0.31	0.12-0.81	0.016
WBC < 50,000/mm ²	0.99	0.41-2.37	NS	0.91	0.38-2.17	NS
WBC \geq 50,000/mm ²	0.21	0.00-14.72	NS	0.01	0.00-36.30	NS
PB blast % \leq median	0.30	0.09-0.97	0.044	0.24	0.07-0.81	0.022
PB blast % > median	1.12	0.43-3.22	NS	1.61	0.55-4.71	NS
BM blast % \leq median	0.78	0.27-2.26	NS	0.67	0.23-1.93	NS
BM blast % > median	0.53	0.19-1.52	NS	0.62	0.20-1.90	NS
De novo AML	0.85	0.36-1.98	NS	0.79	0.34-1.84	NS
Secondary AML	0.01	0.00-40.75	NS	0.01	0.00-246.87	NS
LDH (U/L) \leq 700	0.62	0.25-1.56	NS	0.56	0.22-1.41	NS
LDH (U/L) > 700	0.63	0.17-2.40	NS	0.91	0.23-3.67	NS
N of consolidation Tx. = 1	0.14	0.03-0.70	0.017	0.14	0.03-0.69	0.016
N of consolidation Tx. > 1	0.87	0.43-2.73	NS	1.11	0.43-2.88	NS

OS, overall survival; LFS, leukemia free survival; HR, Hazard ratio; CI, confidence interval; NS, not significant; WBC, white blood cell; PB, peripheral blood; BM, bone marrow; AML, acute myeloid leukemia; LDH, lactate dehydrogenase; Tx., therapy.

eral previous studies demonstrated the clinical benefit of cytarabine-based maintenance therapy (12, 19, 20), these results were inconsistent (21-23). However, our data indicated that oral maintenance therapy with 6MP and MTX prolonged the OS and LFS in AML patients. Moreover, the benefit was more prominent during and early after maintenance therapy.

Not all patients have experienced clinical benefit from maintenance therapy, even those with APL (24-26). In one AML study, clinical benefit from maintenance therapy with tipifarnib, farnesyltransferase inhibitor was observed only in patients with secondary AML or AML with adverse cytogenetics (27). In the present study, patients with intermediate risk cytogenetics achieved more prominent OS and LFS benefits from maintenance thera-

py, whereas patients with favorable cytogenetics received no additional benefits from maintenance therapy. Older patients (Age \geq 60), patients with low PB blast count, and patients who received insufficient consolidation therapy (\leq 1 cycle) obtained prominent clinical benefits from maintenance therapy. Therefore, risk-adapted maintenance therapy in AML patients may be a more appropriate approach, consistent with previous studies (26, 27).

As results from previous trials with conventional chemotherapy-based therapy have been regarded as negative in supporting maintenance therapy, many ongoing clinical trials have been designed with immunotherapy, demethylating therapy, or targeted therapy (14). However, it is notable that among studies

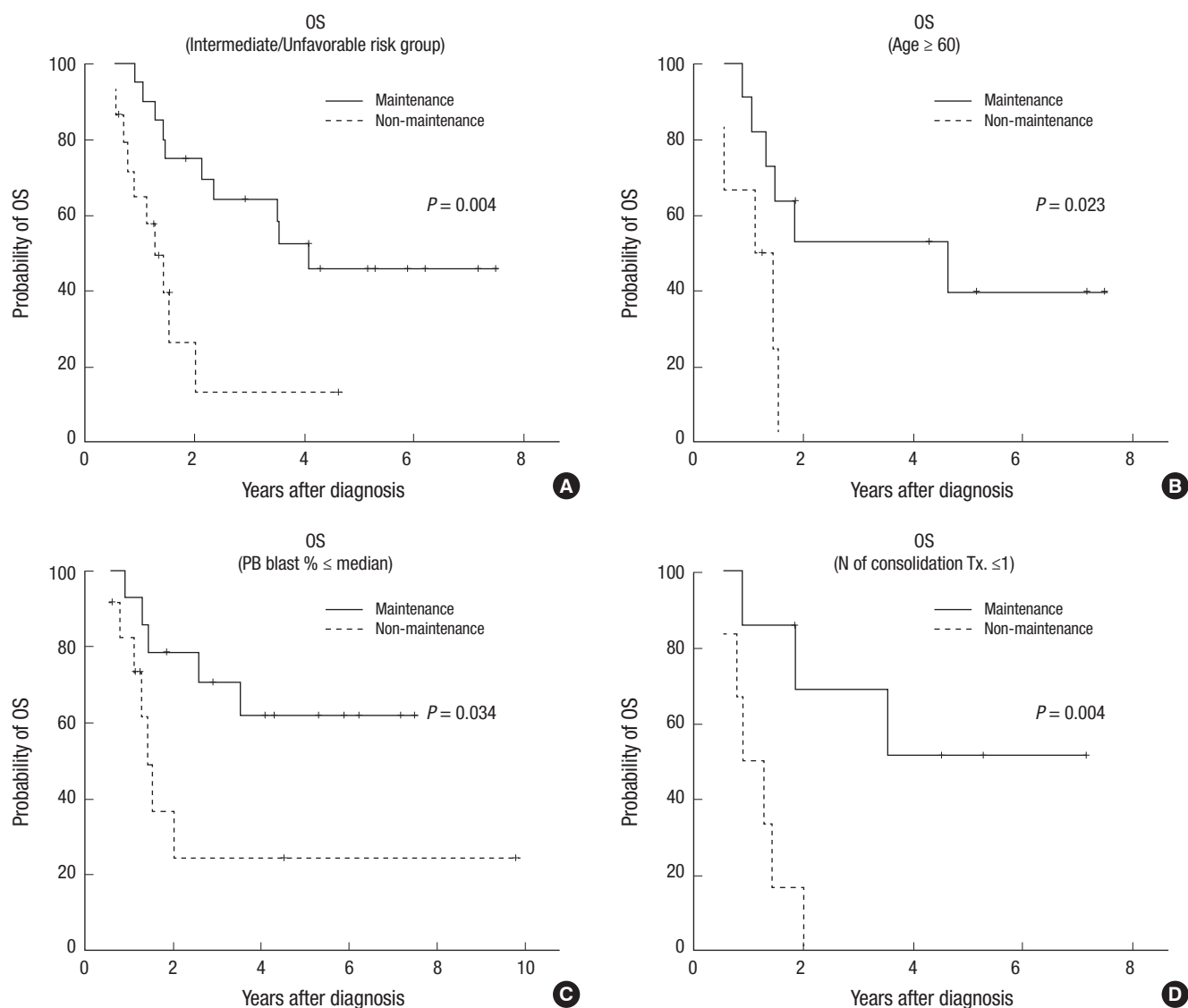


Fig. 2. Overall survival (OS) of patients with risks by the presence or absence of maintenance therapy. (A) OS of those with intermediate or unfavorable cytogenetics, (B) older patients, (C) those with initial low blast count in peripheral blood, (D) those receiving less than two cycles of consolidation therapy.

using maintenance chemotherapy, those using identical consolidation regimens followed by a randomization to maintenance or no maintenance chemotherapy are rare (28). As the pharmacodynamic and pharmacokinetic features and toxicity profile of conventional agents are well known and cost effective, chemotherapeutic agents such as 6MP and MTX are good candidates for further studies about the validation of clinical efficacy as maintenance chemotherapy.

The duration of maintenance therapy is another issue. In the present study, the OS of the maintenance and non-maintenance groups was 66.5% and 45.2%, respectively, within two years, which was the period of maintenance therapy. However, five-year OS was similar between the two groups. Further studies are needed to prove that prolonged exposure to maintenance therapy is more effective and safe. Exposure to anti-cancer drugs during

the two years did not evoke secondary malignancy in our result. To our knowledge, this study is the first report about the clinical outcome of oral maintenance chemotherapy with 6MP and MTX in AML patients. However, the present study has several limitations. First, although patients were well balanced for age, cytogenetics, and prevalence of secondary AML, this study is a retrospective non-randomized study from a single institution. Second, although AML with normal karyotype is a heterogeneous group according to molecular alteration (5), AML with normal karyotype was simply classified and analyzed as an intermediate risk group, as measuring such molecular abnormalities was not routine practice throughout the duration of the study.

In conclusion, oral maintenance therapy prolonged the median OS (43 months vs. 19 months) in AML patients. Given that most AML patients in CR after several cycles of consolidation

therapy experience relapse, the clinical efficacy of maintenance therapy to reduce the relapse from dormant leukemic cells needs to be reconsidered and verified by prospective randomized trials. Nonetheless, the present study suggests that AML patients, especially older patients (≥ 60 yr), those with intermediate or unfavorable cytogenetic results, those with initially low PB blast count ($\%, \leq$ median), and those receiving less than two cycles of consolidation therapy, could benefit from maintenance therapy with 6MP and MTX without incurring clinically or biologically significant adverse events.

DISCLOSURE

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTION

Study design and literature review: Park JS, Jeong SH, Choi YW, Ahn MS, Lee HW, Kang SY, Choi JH. Data management and analyses: Choi YW, Jeong SH, Park JS. Interpretation of findings and writing manuscript: Choi YW, Jeong SH, Park JS

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