Open Access Full Text Article

ORIGINAL RESEARCH

A comparative study of idarubicin 12 mg/m^2 and 8 mg/m^2 combined with cytarabine as the first induction regimen for adult acute myeloid leukemia patients

Li Zhou
Xin Liu
Huilan Liu
Weibo Zhu
Xiaoyan Cai
Kaidi Song
Changcheng Zheng
Baolin Tang
Zimin Sun

Department of Hematology, Anhui Provincial Hospital, Hefei, Anhui, People's Republic of China

Objective: This study aimed to explore a suitable dose of idarubicin (IDA) combined with cytarabine for the initial induction regimen for acute myeloid leukemia (AML) patients.

Patients and methods: A total of 100 adult patients with de novo AML aged between 14 years and 80 years were enrolled in the current study and randomized into two arms for the initial induction: an IDA 12 mg/m^2 arm and an IDA 8 mg/m^2 arm. All patients received the same consolidation chemotherapy. The follow-up period was January 1, 2009, to December 31, 2014. Overall survival (OS), disease-free survival (DFS), and morphology leukemia relapse (hematological and/or extramedullary) were recorded.

Results: The complete remission rates were 80% and 75% in the IDA 12 mg/m^2 and IDA 8 mg/m^2 arms, respectively, after initial induction. High-dose IDA (12 mg/m^2) resulted in a higher complete remission rate after two courses of induction therapy (96.4% vs 76.5%) in the cytogenetic intermediate-risk group (P=0.026). There were no differences in the number of units of infused red blood cells, agranulocytosis time, or infection rates between the two arms. Patients in the IDA 12 mg/m^2 arm received more platelet transfusions (P=0.047). In the intention-to-treat analysis, after a median follow-up of 13 months, high-dose IDA (12 mg/m^2) resulted in improved OS (median OS, 54.0 months vs 26.7 months, P=0.021) and DFS (median DFS, 54.0 months vs 18.3 months, P=0.031), particularly in the cytogenetic intermediate-risk group (median OS, 54.0 months vs 29.5 months, P=0.009; median DFS, 54.0 months vs 15.3 months, P=0.014). IDA 12 mg/m^2 significantly improved OS and DFS in the cytogenetic intermediate-risk group (P=0.009 and P=0.018).

Conclusion: Our results suggest that a high dose of IDA (12 mg/m^2) combined with cytarabine is a suitable and safe initial remission induction regimen that results in superior long-term survival of adult AML patients, particularly patients in the cytogenetic intermediate-risk group.

Keywords: idarubicin, acute myeloid leukemia, disease-free survival, overall survival

Introduction

The main goals of initial induction chemotherapy for acute myeloid leukemia (AML) are rapid disease control through achievement of complete remission (CR), long-term survival, and low relapse rates with minimal induction toxicity. The 7+3 regimen combining an anthracycline (daunorubicin [DNR]) with cytarabine has formed the backbone of AML induction for decades. Modification of DNR 45 mg/m^2 to idarubicin (IDA) 12 mg/m^2 has resulted in an improved curative effect and fewer adverse events.[1,2] In 2010, the National Comprehensive Cancer Network (NCCN) recommended IDA 12 mg/m^2 as the first-line induction dosage. However, it remains unclear if the

Correspondence: Zimin Sun
Department of Hematology, Anhui Provincial Hospital, No 17 Lujing Road, Hefei, Anhui, People's Republic of China
Tel +86 136 0551 8126
Fax +86 551 6228 3306
Email zmsun_vip@163.com

increased dose of IDA is positively correlated with superior efficacy. Pautas et al reported no significant differences in relapse incidence, event-free survival, or overall survival (OS) among IDA3 (12 mg/m^2 ×3) and IDA4 (12 mg/m^2 ×4) arms of the ALFA-9801 study.[3] The Chinese clinical practice guidelines for AML (nonacute promyelocytic leukemia; 2011 edition) recommended IDA 8–12 mg/m^2 combined with cytarabine as the initial 3 days idarubicin and 7 days cytarabine regimen for adult AML patients. However, there are no data indicating whether IDA 12 mg/m^2 is superior to IDA 8 mg/m^2. This study aimed to explore a suitable dose of IDA combined with cytarabine as the first induction regimen for adults with AML by comparing the treatment effects and adverse reactions of IDA 12 mg/m^2 and IDA 8 mg/m^2.

Patients and methods

A total of 100 cases of adult de novo acute AML (excluding acute promyelocytic leukemia) were enrolled in the current study at the Department of Hematology of Anhui Provincial Hospital from January 1, 2009, to June 30, 2014. The patients were randomized into two arms: the IDA 12 mg/m^2 arm and the IDA 8 mg/m^2 arm. The diagnosis of AML was based on WHO criteria, and AML was classified according to the French–American–British classification. The cytogenetic prognostic grouping criteria were classified according to the NCCN clinical practice guidelines for AML (nonacute promyelocytic leukemia; 2008 edition). All the patients were diagnosed as de novo AML. The patients were eligible for inclusion in the study if they were 14–80 years of age, had a pathologically confirmed diagnosis, and had at least 20% myoblasts in the bone marrow. Bone marrow smears from all patients were examined by May–Giemsa staining. Cytogenetic abnormalities were detected by conventional G banding.[4] We stratified the patients into risk groups based on cytogenetic and molecular analyses of bone marrow samples collected at diagnosis prior to any treatment according to the NCCN clinical practice guidelines for AML.[5]

Induction therapy included a standard IA regimen (IDA 12 mg/m^2 once daily intravenously [iv] from days 1 to 3 combined with cytarabine 100 mg/m^2 once daily continuous iv from days 1 to 7).[1] A low-dose IA regimen was also used (IDA 8 mg/m^2 once daily iv from days 1 to 3 combined with cytarabine 100 mg/m^2 once daily continuous iv from days 1 to 7). The patients received another IA regimen if they did not achieve CR. Subsequently, four to six courses of intermediate-dose cytarabine (1–2 g/m^2 twice daily iv over 3 hours from days 1 to 3) were administered as consolidation chemotherapy. Patients in adverse cytogenetic group who were in CR after consolidation chemotherapy and who had an HLA-matched donor could undergo allogeneic stem cell transplantation. Follow-up was performed until December 31, 2014.

The study protocol samples were approved by the ethics committee of Anhui Provincial Hospital and were conducted in accordance with the Declaration of Helsinki. All the patients gave written informed consent.

Definitions and study end points

The primary end points were OS, disease-free survival (DFS), and morphology leukemia relapse (hematological and/or extramedullary). OS was defined as the duration from diagnosis to death from any cause, and DFS was defined as the time from achieving CR until relapse or death. For analyses of DFS, failures were considered clinical or hematological relapse or deaths from any cause; patients alive and in CR were censored at the last follow-up. For analyses of OS, failures were considered death from any cause; alive patients were censored at the date of last contact. A secondary end point was the comparison of CR rates in the two study arms.

Statistical analyses

The data in our study were statistically analyzed using the Statistical Package for Social Science (SPSS version 19.0; IBM Corporation, Armonk, NY, USA) and R 2.10.1 (Lucent Technologies, Muray Hill, NJ, USA). Statistical significance was considered at P-values <0.05. All reported P-values are two sided. Differences in continuous variables were analyzed by two independent samples t-tests and chi-square tests; Fisher's exact test was performed to compare incidences. The Kaplan–Meier method and life table were performed to estimate the survival probabilities, and a log-rank test was used for univariate comparison.[6] Cumulative incidence curves for nonrelapse mortality and relapse with or without death were constructed reflecting time to relapse and time to nonrelapse mortality as competing risks. OS and DFS were compared using a log-rank test and a Cox proportional hazards model.

Results

Patient characteristics

The current study comprised 100 de novo AML patients, including 57 males and 43 females. The demographic and disease characteristics of the patients are listed in Table 1. The median age of the patients was 44 years (range 14–77 years). There were 45 patients in the 12 mg/m^2 arm, 25 males and 20 females, with an age range of 14–77 years and a median age of 42 years. There were 55 patients in the 8 mg/m^2 arm,

Table 1 Patient characteristics

Characteristics	Overall (n=100)	Treatment arm		P-value
		IDA 12 mg/m² (N=45)	IDA 8 mg/m² (N=55)	
Age (years)		41.87±13.84	42.84±14.50	0.781
<55	79 (79%)	35 (77.8%)	44 (80%)	0.938
≥55	21 (21%)	10 (22.2%)	11 (20%)	
WBC at diagnosis (×10⁹/L)		34.42±45.78	34.51±65.23	0.195
<10×10⁹/L	43 (43%)	20 (44.4%)	23 (41.8%)	0.792
≥10×10⁹/L	57 (57%)	25 (55.6%)	32 (58.2%)	
Sex, n (%)				
Male	57 (57)	25 (55.6)	32 (58.2)	P=1.0
Female	43 (43)	20 (44.4)	23 (41.8)	
FAB, n (%)				
M0	2 (2)	2 (4.4)	0 (0)	P=0.055
M1	8 (8)	4 (8.8)	4 (7.2)	
M2	30 (30)	9 (20)	21 (38.2)	
M4	6 (6)	3 (6.7)	3 (5.5)	
M5	40 (40)	16 (35.6)	24 (43.6)	
M6	4 (4)	3 (6.7)	1 (1.8)	
M7	1 (1)	0 (0)	1 (1.8)	
Myeloid sarcoma	3 (3)	3 (6.7)	0 (0)	
Unclassified AML	6 (6)	5 (11.1)	1 (1.8)	
Cytogenetic group, n (%)				
Favorable	13 (13)	8 (17.8)	5 (9.1)	P=0.324
Intermediate	62 (62)	28 (62.2)	34 (61.8)	
Adverse	25 (25)	9 (20)	16 (29.1)	
SCT, n (%)	6 (6)	3 (6.7)	3 (5.5)	P=0.800

Note: Age and WBC are presented as the mean ± standard deviation.
Abbreviations: AML, acute myeloid leukemia; FAB, French–American–British; IDA, idarubicin; WBC, white blood cell; SCT, stem cell transplantation.

32 males and 23 females, with an age range of 14–69 years and a median age of 42 years. Of the 100 patients, cytogenetic analysis classified 13 (13%) patients in the favorable group, 62 (62%) patients in the intermediate-risk group, and 25 (25%) patients in the adverse group. The two arms were well balanced with regard to pretreatment characteristics such as age, white blood cell count, prognostic groups, French–American–British classification, and the proportion undergoing sibling allogeneic hematopoietic stem cell transplantation. The median follow-up time of the patients was 13 months (1–70 months; Table 1).

Response to induction therapy

Of the 100 patients, 75 (75%) patients achieved CR after one course of induction chemotherapy and 81 (81%) patients achieved CR after two courses of induction chemotherapy (CR2). In the IDA 12 mg/m² group, 36 of 45 patients achieved CR (incomplete blood count recovery [CRi] one case) after initial induction, with a remission rate of 80%, and 41 (91.1%) of 45 patients achieved CR2. In the IDA 8 mg/m² group, 39 patients (70.9%) of 55 patients achieved CR after initial induction, and 40 (72.7%) of 55 patients

achieved CR2. There was no significant difference in the one-course CR rate or the two-course CR rate between the two arms. The overall response was 88.9% (40 of 45 patients) and 75% (41 of 55 patients) in the two arms. The rate of remission for the two-course induction was 96.4% (27 of 28 patients) in the intermediate cytogenetic risk group in the IDA 12 mg/m² arm, significantly higher than the remission rate of 76.5% (26 of 34 patients) in the IDA 8 mg/m² arm (P=0.026).

Adverse events

All patients experienced severe bone marrow suppression and hematological toxicities. No patients suffered from early death in the IDA 12 mg/m² arm. Two patients died early (within 30 days) in the IDA 8 mg/m² arm. This difference was not statistically significant (P=0.300). The infection rates were 95.6% and 92.3% in the two arms, a difference that was not significant (P=0.439). Meanwhile, there was no significant difference in serious infections such as pulmonary, bloodstream, and fungal infections. The median durations for stable recovery of neutrophils to 0.5×10⁹/L and platelets to 20×10⁹/L were 13 (range: 0–33) days and

11.5 (range: 0–40) days, respectively. The durations were 7 (range: 0–20.5) days and 5 (range: 1–15) days in the IDA 12 mg/m^2 arm and 6 (range: 0–22) days and 2 (range: 0–13) days in the IDA 8 mg/m^2 arm. The numbers of erythrocyte and platelet transfusions were 6 (range: 0–22) units and 3 (range: 0–15) units, respectively, 5 (range: 2–32) units and 10 (range: 2–36) units in the IDA 12 mg/m^2 arm and 11 (range: 0–33) units and 12 (range: 0–40) units in the IDA 8 mg/m^2 arm.

There were no differences in the infused red blood cell count units or agranulocytosis time between the two arms (P=0.242 and P=0.326). The IDA 12 mg/m^2 arm received more platelet transfusions than the IDA 8 mg/m^2 arm (P=0.047). Of the 100 patients, one patient had ventricular arrhythmias, one patient experienced the emergence of drug-induced liver injury, and one patient experienced acute renal failure (Table 2).

Costs of the first regimen reduction chemotherapy

The total hospital charges per patient were 79,365.94± 30,392.62 RMB and 76,984.82±97,031.22 RMB for the IDA 12 mg/m^2 arm and IDA 8 mg/m^2 arm, respectively; the difference between the arms was not statistically significant (P=0.372; Table 2).

Hazard ratios for death

All hazard ratios are for patients who received a 12 mg/m^2 dose of IDA compared with patients who received an 8 mg/m^2 dose. A univariate Cox proportional hazards model was used to estimate the hazard ratios and the significance of the comparison for OS. The model indicated that IDA 12 mg/m^2 was superior to IDA 8 mg/m^2 in long-term survival regardless of older or younger than 55 years of age or achievement of CR

after the first induction. However, IDA 12 mg/m^2 was superior for females, for patients with white cell counts ≥10×10^9/L, and for the adverse group when sex, white cell count, and cytogenetic profile were considered. Multivariate proportional hazards model was used when P<0.1 in univariate Cox proportional hazards model analysis to examine the effect of treatment on OS, with adjustments for sex, age, and cytogenetic profile; older age, an unfavorable cytogenetic profile, and high leukocyte counts were clinically significant risk factors for poor survival. With adjustment for these risk factors as continuous variables, the dose of IDA and age significantly influenced survival as categorical variables (P=0.009, hazard ratio 4.661, 95% CI, 1.460–14.883 and P=0.037, hazard ratio 2.939, 95% CI, 1.069–8.081, respectively). Achieving CR after the first induction also significantly influenced survival (P=0.001, hazard ratio 6.815, 95% CI, 2.131–21.793).

Incidence of relapse and death and treatment-related mortality rate

Of the 81 CR patients who experienced relapse as the first event, five patients belonged to the IDA 12 mg/m^2 arm and 14 patients belonged to the IDA 8 mg/m^2 arm. The 1-year and 2-year relapse rates were 16.2% and 16.2% in the IDA 12 mg/m^2 arm vs 31.8% and 45.1% in the IDA 8 mg/m^2 arm, respectively. There was no significant difference in the cumulative incidence of relapse (P=0.183, by the Gray's test). These results remained unchanged when analyzing the different cytogenetic prognostic groups between the two arms (P=0.950, P=0.301, and P=0.407 for favorable, immediate, and adverse groups, respectively). The 1-year and 2-year nonrelapse mortality rates were 9.25% and 9.25% in the IDA 12 mg/m^2 arm vs 19.0% and 19.0% in the IDA 8 mg/m^2 arm, respectively. There was no significant difference between the IDA 12 mg/m^2 and IDA 8 mg/m^2 arms

Table 2 Adverse events after the start of induction therapy

	IDA 12 mg/m^2 arm (N=45)	IDA 8 mg/m^2 arm (N=55)	P-value
Infection, n (%)	43 (95.6)	51 (92.7)	0.439
Pulmonary infection, n (%)	22 (48.9)	37 (67.2)	0.063
Bloodstream infection, n (%)	4 (8.89)	5 (9.09)	0.502
Fungal infection, n (%)	6 (13.3)	10 (18.2)	0.511
Infusion of RBC (μ), mean ± SD	7.53±5.68	6.02±5.11	0.242
Infusion of PLT (μ), mean ± SD	5.47±3.07	3.07±2.67	0.047
Duration of neutropenia (days), mean ± SD	16.16±7.72	12.82±7.30	0.330
Duration of PLT <20×10^9 (days), mean ± SD	12.11±7.14	13.15±8.82	0.297
Acute cardiac toxicity, n (%)	1 (2.2)	0 (0)	0.450
Early death[a], n (%)	0 (0)	2 (3.63)	0.300
Economic cost (RMB, Yuan), mean ± SD	79,365.93±30,392.61	76,984.8±97,031.22	0.372

Notes: Duration of neutropenia (days), infusion of RBC, and infusion of PLT are presented as mean ± standard deviation. [a]Death within 30 days after the start of induction therapy.
Abbreviations: IDA, idarubicin; PLT, platelet; RBC, red blood cell.

(P=0.0658, by the Gray's test). However, mortality rates significantly higher in the immediate-risk cytogenetic group in the IDA 8 mg/m^2 arm (0 vs 23.2%, P=0.01, by the Gray's test). The 1-year treatment-related mortality rates were 3.0% and 17.0% (P=0.040, by the Gray's test), and the 2-year treatment-related mortality rates were 9.3% and 15.1% in the two arms (P=0.160, by the Gray's test).

OS and DFS

After a median follow-up of 13 (1–70) months from diagnosis until December 31, 2014, the 1-year and 2-year expected OS rates were 83.0% and 83.0%, respectively, in the IDA 12 mg/m^2 arm. The rates were 79.0% and 40.0% in the IDA 8 mg/m^2 arm. The median OS was 54.0 months vs 26.7 months in the two arms (P=0.021, by log-rank test; Table 3). The 1-year and 2-year expected DFS were 75.0% and 67.0% in the IDA 12 mg/m^2 arm and 51.0% and 36.0% in the IDA 8 mg/m^2 arm, respectively. The median DFS was 54.0 months vs 18.3 months (P=0.031, by log-rank test) in the two arms (Table 3).

Effect of cytogenetic profile

The CR rates for the favorable, intermediate-risk, and adverse groups were 92.3%, 77.4%, and 60%, respectively (P=0.072 for overall comparisons). The expected OS rate was higher in the IDA 12 mg/m^2 arm than in the cytogenetic intermediate-risk group. The median OS was 54.0 months vs 29.5 months (P=0.009, by log-rank test; Table 3). The median DFS was 54 months vs 15.3 months in the two arms in the cytogenetic intermediate-risk group (P=0.018, by log-rank test; Table 3). The worst outcome was observed in the subgroup with an adverse cytogenetic profile; the median survival was 20.2 months and 18.9 months for the two treatment arms, a difference that was not significant (P=0.914, by log-rank test). However, the interaction between the

treatment assignment and the cytogenetic profile was not significant.

Effect of age

For the people younger than 55 years, the OS of patients in the 12 mg/m^2 arm was significantly longer than in the 8 mg/m^2 arm (P=0.017, by log-rank test). For the people older than 55 years, there is a trend that the OS of patients in the 12 mg/m^2 arm was longer than in the 8 mg/m^2 arm, but there is no statistically significant difference of OS between these two dose arms (P=0.364, by log-rank test).

Discussion

It has been postulated that one of the most effective ways to achieve higher CR rates and OS among patients with AML is to increase the induction dose of anthracyclines.[7] Trials of various chemotherapeutic agents have reported an improved CR rate among patients receiving high-dose DNR.[8,9] Several trials have compared IDA and DNR, but only a few studies have focused on the dose of IDA. In this trial, we evaluated the effect of IDA dose intensity on remission induction in patients with de novo AML.

In our study, the CR rate was higher in the IDA high-dose arm than in the low-dose arm. However, this difference was not significant, and a larger patient sample may be needed. The CR rates attained in this trial were higher than those observed in previous studies such as the ECOG study, which used DNR and contained more patients older than 50 years.[10] However, the CR rates observed in the present study are similar to those reported in the ALFA-9801, AML-92, and JALSG AML201 studies.[3,11,12] Pautas et al reported an overall CR rate of 77%, with significant differences among the three arms (IDA3 [12 mg/m^2 X3], IDA4 [12 mg/m^2 X4], and DNR [80 mg/m^2 X3]) in the ALFA-9801 study. No significant differences in relapse incidence, event-free survival, or OS

Table 3 Media OS or DFS of patients

Induction treatment	Total (mo)	Deaths (mo)	Censored (mo)	Median OS (mo)	Median DFS (mo)
Media OS or DFS of total patients in 12 mg/m^2 and 8 mg/m^2 arms					
IDA 12 mg/m^2 arm[a]	45	4	41	54	
IDA 8 mg/m^2 arm[a]	55	16	39	26.7	
IDA 12 mg/m^2 arm[a]	45	8	37		54
IDA 8 mg/m^2 arm[a]	55	21	34		18.3
Media OS and DFS of patients with an intermediate cytogenetic profile					
IDA 12 mg/m^2 arm[b]	31	1	30	54	
IDA 8 mg/m^2 arm[b]	36	11	25	29.5	
IDA 12 mg/m^2 arm[b]	31	4	27		54
IDA 8 mg/m^2 arm[b]	36	15	21		15.3

Notes: Kaplan–Meier estimates of overall survival data and disease-free survival data from the intention-to-treat analysis are shown for [a]survival of all patients, [b]those with an intermediate cytogenetic profile.
Abbreviations: DFS, disease-free survival; IDA, idarubicin; mo, months; OS, overall survival.

were observed among the three arms.[3] In the present study, the CR rate was clearly higher for the two courses of high-dose IDA than for the low dose, indicating a stronger effect of high-dose IDA in refractory AML patients. In the adverse group, the CR2 rate was higher in the IDA 12 mg/m^{2} arm. The failure to observe a significant difference may be due to an insufficient number of cases; in our study, we had only 15 cases in the cytogenetic adverse group. IDA decreased the proportion of patients with resistant disease after induction, particularly in the immediate-risk group. Carella et al reported similar results in 1993; IDA in combination with intermediate-dose cytarabine and VP-16 had a good effect in refractory or rapidly relapsed AML patients.[13]

The higher dose of 12 mg/m^{2} of IDA did not significantly increase the frequency of adverse events or the hospital cost of induction therapy. Taken together, however, the present study and previous studies do not provide definitive proof that an increased dose of IDA improves CR rates. Pashko et al evaluated the cost of 120 untreated AML patients randomly assigned to receive 12 mg/m^{2} of IDA or 50 mg/m^{2} of DNR daily for 3 days with 200 mg/m^{2} of cytosine arabinoside daily for 5 days. The costs per CR and per year of survival were lower for the IDA patients than for the DNR patients. We observed similar results in the present study. The cost of the first remission induction therapy did not differ between the two dosage arms. The hospital charges per year of survival were not evaluated but should be lower in the IDA 12 mg/m^{2} arm due to the longer survival of patients in this arm. Pashko et al suggested that the lower remission rate in DNR-treated patients and their consequent need for additional care would increase the cost differences between the two treatments. IDA is more cost-effective than DNR for the treatment of adult AML.[14]

In our study, lower relapse incidence and no-relapse mortality were observed after timed sequential induction in the IDA high-dose arm. The failure to observe a significant difference may be due to an insufficient number of cases or the short flow up.

In the present study, we observed significant improvements in OS among patients who received high-dose 12 mg/m^{2} of IDA compared with low-dose 8 mg/m^{2} of IDA. Patients with intermediate cytogenetic profiles fared well in the high-dose arm, with significantly longer survival compared with those in the low-dose arm. At the time of the final analysis, the largest survival difference between the two treatment arms was observed in the subgroup of patients with intermediate cytogenetic risk. However, there was no survival difference

between the two dose arms in the favorable cytogenetic subgroups. We conclude that in patients with favorable risk, 8 mg/m^{2} can be used for induction treatment. In the ECOG trial, Fernandez et al conducted a Phase III randomized trial of 657 de novo AML patients between the ages of 17 years and 60 years to receive three once daily doses of DNR 90 mg/m^{2} vs 45 mg/m^{2} combined with seven daily doses of cytarabine 100 mg/m^{2} by continuous iv infusion. The high dose of DNR improved the rate of CR and the duration of OS. The high dose was also superior for intermediate cytogenetic profiles but unfavorable for low-risk cytogenetic profiles.[15] This outcome is consistent with our results. For patients with intermediate-risk disease, physicians could safely use anthracycline intensification of 12 mg/m^{2} of IDA (by either cytarabine intensification or stem cell transplantation) and anticipate excellent outcomes. A high dose of IDA provided no benefit in some of the patients in adverse cytogenetic profile in our study. The result is similar to the outcomes of the ECOG trial.[16] Other treatments were required for the adverse group, because the elevated dose did not change long-term survival. For the elderly patients, there is a trend that the OS of patients in 12 mg/m^{2} arm was longer than that in 8 mg/m^{2} arm in our study, but there is no statistically significant difference probably because of the rare case. Some other studies thought that a reduced dose might be superior. Flasshove et al observed improved OS at 5 years for patients up to 50 years of age vs patients older than 50 years of age and improved DFS and OS with a normal (vs unfavorable) karyotype.[17] A Japanese study examined the effect of decreased-dose IDA (12 mg/m^{2} X2) for elderly AML patients and observed an improved 2-year OS rate and lower 2-year relapse-free survival among elderly patients of 65–74 years of age compared with younger patients, which suggests that elderly patients would benefit from a reduced dose of IDA.[18] The results of these two studies are not consistent with our results. Considering that we only have 10 and 11 patients in these two arms, further study needs to be done with more patients.

Our study suggests that IDA 12 mg/m^{2} combined with cytarabine is a suitable regimen for initial remission induction treatment in adults with de novo AML (nonacute promyelocytic leukemia). The IDA 12 mg/m^{2} dose is safe without significant adverse reactions. The regimen was well tolerated by the patients and did not result in increased hospital costs. The 12 mg/m^{2} dose of IDA confers improved long-term survival and DFS and particularly improves the prognosis of patients with cytogenetic intermediate-risk profiles compared with a dose of 8 mg/m^{2}.

Acknowledgment

Disclosure

The authors report no conflicts of interest in this work.

References

1. Berman E, Heller G, Santorsa J, et al. Results of a randomized trial comparing idarubicin and cytosine arabinoside with daunorubicin and cytosine arabinoside in adult patients with newly diagnosed acute myelogenous leukemia. *Blood*. 1991;77:1666–1674.
2. Wiernik PH, Banks PL, Case DC Jr, et al. Cytarabine plus idarubicin or daunorubicin as induction and consolidation therapy for previously untreated adult patients with acute myeloid leukemia. *Blood*. 1992;79: 313–319.
3. Pautas C, Merabet F, Thomas X, et al. Randomized study of intensified anthracycline doses for induction and recombinant interleukin-2 for maintenance in patients with acute myeloid leukemia age 50 to 70 years: results of the ALFA-9801 study. *J Clin Oncol*. 2010;28(5):808–814.
4. Dohner H, Estey EH, Amadori S, et al; European LeukemiaNet. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood*. 2010;115(3):453–474.
5. O'Donnell MR, Abboud CN, Altman J, et al. Acute myeloid leukemia. *J Natl Compr Canc Netw*. 2012;10(8):984–1021.
6. Meng FT, Wang YL, Liu J, Zhao J, Liu RY, Zhou JN. ApoE genotypes are associated with age at natural menopause in Chinese females. *Age (Dordr)*. 2012;34(4):1023–1032.
7. Rowe J, Tallman MS. Intensifying induction therapy in acute myeloid leukemia: has a new standard of care emerged? *Blood*. 1997;90(6): 2121–2126.
8. Bishop JF, Matthews JP, Young GA, Bradstock K, Lowenthal RM. Intensified induction chemotherapy with high dose cytarabine and etoposide for acute myeloid leukemia: a review and updated results of the Australian Leukemia Study Group. *Leuk Lymphoma*. 1998;28(3–4): 315–327.
9. Weick JK, Kopecky KJ, Appelbaum FR, et al. A randomized investigation of high-dose versus standard-dose cytosine arabinoside with daunorubicin in patients with previously untreated acute myeloid leukemia: a Southwest Oncology Group Study. *Blood*. 1996;88(8):2841–2851.
10. Wahlin A, Billstrom R, Bjor O, et al. Results of risk-adapted therapy in acute myeloid leukaemia. A long-term population-based follow-up study. *Eur J Haematol*. 2009;83(2):99–107.
11. Koistinen P, Raty R, Itala M, et al; Finnish Leukaemia Group. Long-term outcome of intensive chemotherapy for adults with de novo acute myeloid leukaemia (AML): the nationwide AML-92 study by the Finnish Leukaemia Group. *Eur J Haematol*. 2007;78(6):477–486.
12. Ohtake S, Miyawaki S, Fujita H, et al. Randomized study of induction therapy comparing standard-dose idarubicin with high-dose daunorubicin in adult patients with previously untreated acute myeloid leukemia: the JALSG AML201 study. *Blood*. 2011;117(8):2358–2365.
13. Carella AM, Carlier P, Pungolino E, et al. Idarubicin in combination with intermediate-dose cytarabine and VP-16 in the treatment of refractory or rapidly relapsed patients with acute myeloid leukemia. The GIMEMA Cooperative Group. *Leukemia*. 1993;7(2):196–199.
14. Pashko S, Jacobs J, Santorsa J. The cost-effectiveness of idarubicin/cytosine arabinoside versus daunorubicin/cytosine arabinoside in the treatment of adults with acute myeloid leukemia. *Clin Ther*. 1991;13(3): 353–360.
15. Fernandez HF, Sun Z, Yao X, et al. Anthracycline dose intensification in acute myeloid leukemia. *N Engl J Med*. 2009;361(13):1249–1259.
16. Löwenberg BO, Ossenkoppele GJ, van Putten W, et al; Dutch-Belgian Cooperative Trial Group for Hemato-Oncology (HOVON); German AML Study Group (AMLSG); Swiss Group for Clinical Cancer Research (SAKK) Collaborative Group. High-dose daunorubicin in older patients with acute myeloid leukemia. *N Engl J Med*. 2009;361(13):1235–1248.
17. Flasshove M, Meusers P, Schütte J, et al. Long-term survival after induction therapy with idarubicin and cytosine arabinoside for de novo acute myeloid leukemia. *Ann Hematol*. 2000;79(10):533–542.
18. Kobayashi T, Ichikawa M, Nannya Y, Kurokawa M. The effect of decreased-dose idarubicin for elderly patients with acute myeloid leukemia. *Jpn J Clin Oncol*. 2013;43(10):1047–1051.