Table 3. IAG regimen: non-hematological toxicities

	Level 1 (n = 3)	Level 2 (n = 3)	Level 3 (n = 3)
Febrile neutropenia (grade 0/3/4)	0/3/0	1/2/0	0/2/1
Sepsis (grade 4)	0	0	1
Cerebral abscess (grade 4)	0	0	1
Hepatic toxicity (grade 0/1/2/3)	2/0/1/0	2/0/1/0	1/0/1/1
Nausea and vomiting (grade 0/1/2/3)	3/0/0/0	3/0/0/0	1/0/2/0
Diarrhea (grade 0/1/2/3)	3/0/0/0	3/0/0/0	2/1/0/0
Edema (grade 0/1/2/3)	3/0/0/0	3/0/0/0	2/1/0/0
Skin rash (grade 0/1/2/3)	3/0/0/0	3/0/0/0	2/0/1/0
VOD/SOS	0	0	0

SOS, sinusoidal obstructive syndrome; VOD, veno-occlusive disease.

was observed in all patients. Days to nadir of ANC after GO administration were 5–13 days, and days toward ANC-recovery were 24–42 days. As one patient in level 3 (IPt-7) did not recover from neutropenia for 42 days (6 weeks), we regarded this prolongation of neutropenia as a DLT.

All patients had grade 4 thrombocytopenia and required plenty of PLT transfusion. Some patients took more than 30 days to recover to at least the initial level of PLT. As one patient in level 3 (IPt-8) required 220 units of PLT transfusion and took 87 days for recovery without disease progression, we regarded this prolongation of thrombocytopenia as a DLT.

Among non-hematological toxicities (Table 3), febrile neutropenia (FN) was common and severe. One patient in level 3 (IPt-9), although eventually recovered and attained CR, suffered from grade 4 neutropenia, sepsis and brain abscess. We regarded this FN with an infectious episode as a DLT.

Most non-hematological toxicities other than FN were clinically manageable and none of the patients had grade 4 hepatic toxicity, veno-occlusive disease (VOD) or sinusoidal obstructive syndrome (SOS).

In the DAG regimen. Grade 4 leukopenia and neutropenia was observed in all patients (Table 4). All except one patient in level 2 (DPt-6) recovered within 5 weeks. Grade 3/4 of thrombocytopenia was also observed in all patients, and plenty of PLT transfusion was required. The majority of patients recovered from thrombocytopenia within 5 weeks except one patient (DPt-6) who died of central nervous system (CNS) bleeding due to progression of leukemia within 30 days. The patient, DPt-6, was a 60-year-old man who was refractory to initial induction therapy. His leukemic blasts were reduced 47% in his bone marrow

(BM) on day 15 of DAG level 2 (10 days after GO) and 4% in his peripheral blood (PB) on day 19. However, the duration of his response was short as his blasts rapidly increased to 85.2% in the BM on day 23 and 57% in PB on day 26. He suffered from disseminated intravascular coagulation (DIC) and eventually CNS bleeding on day 26, although the platelet count was maintained at $>40 \times 10^9$/L. Autopsy confirmed that progression of leukemia was the cause of his death without any clinical effect of the chemotherapy.

Among the non-hematological toxicities (Table 5), although FN was common and severe, none of the patients developed fatal infection, or had VOD or SOS. None of the grade 4 non-hematological toxicities developed either. As all patients in level 3 of the IAG regimen had DLT as mentioned above, the safety review board (SRB) recommended that level 4 of the DAG should be cancelled, because 5 mg/m² GO would be too toxic in combination with chemotherapy. Our previous study[4] indicated that the dose and schedule of DNR of level 3 of the DAG is equally effective and intensive as those of IDR of levels 2 and 3 in the IAG. Therefore, we considered that adding 5 mg/m² of GO to DNR + Ara-C (level 4 of the DAG) would be as toxic as level 3 of IAG, and accepted the recommendation of the SRB.

Antileukemic activity. A CR was achieved in nine of 19 patients and one attained a CRp, making the overall response rate 52.6%. In addition, two patients obtained partial remission, and four patients showed blast clearance, but three patients were resistant to therapy (Table 6). CR/CRp was observed in all levels of IAG and DAG. A CR was obtained in two patients with adverse karyotypes such as t(6:9) and complex. The rate of

Table 4. DAG regimen: hematological toxicities

	Level 1 (n = 3) (DPt-1/DPt-2/DPt-3)	Level 2 (n = 4) (DPt-4/DPt-5/DPt-6/DPt-7)	Level 3 (n = 3) (DPt-8/DPt-9/DPt-10)
WBC (×10⁹/L) at GO administration	1.1/1.2/0.7	2.4/1.7/0.5/0.3	0.6/1.7/2.0
WBC (grade 3/4)	0/3	0/4	0/3
Days to nadir after GO administration	7/10/7	7/11/3/8	3/5/7
ANC (×10⁹/L) at GO administration	0.4/0.6/0.2	0.2/1.3/0.2/0.0	0.4/1.0/1.2
ANC (grade 3/4)	0/3	0/4	0/3
Days to nadir after GO administration	7/8/7	11/13/5/8	7/7/12
Days toward ANC recovery	26/29/33	23/18/NA/28	34/24/26
PLT (×10⁹/L) at GO administration	361/47/122	71/199/53/3	32/147/193
PLT (grade 3/4)	2/1	3/1	3/0
Days to nadir after GO administration	11/11/17	13/13/17	14/8/17
PLT transfusion (units)	150/60/90	50/70/110/170	170/60/40
Days toward PLT recovery	22/39/31	32/20/NA/26	28/29/21
Hemoglobin (grade 0/1/2/3/4)	0/3/0/0/0	2/1/1/0/0	0/1/2/0/0
RBC transfusion (units)	18/0/6	0/6/10/10	6/6/8

ANC, neutrophils; NA, data was not available because of central nervous system bleeding due to disease progression before ANC and PLT recovery; PLT, platelets; RBC, red blood cells; WBC, leukocytes.

Table 5. DAG regimen: non-hematological toxicities

Toxicity	Level 1 (n = 3)	Level 2 (n = 4)†	Level 3 (n = 3)
Febrile neutropenia (grade 0/3/4)	0/2/1	1/3/0	1/2/0
Hepatic toxicity (grade 0/1/2/3)	2/0/1/0	3/0/1/0	1/1/1/0
Nausea and vomiting (grade 0/1/2/3)	2/0/1/0	4/0/0/0	2/0/1/0
Colitis (grade 0/1/2/3)	2/0/1/0	4/0/0/0	3/0/0/0
Diarrhea (grade 0/1/2/3)	3/0/0/0	4/0/0/0	2/0/1/0
Cardiac (grade 0/1/2/3)	3/0/0/0	3/0/1/0	2/0/1/0
VOD/SOS	0	0	0

†One patient in level 2 died of CNS bleeding due to disease progression. SOS, sinusoidal obstructive syndrome; VOD, veno-occlusive disease.

Table 6. Response

	IAG regimen			DAG regimen			Overall	
	Level 1 (n = 3)	Level 2 (n = 3)	Level 3 (n = 3)	Level 1 (n = 3)	Level 2 (n = 4)	Level 3 (n = 3)	(n = 19)	
CR	1	2	1	1	3	1	9 }	52.6%
CRp			1				1 }	
PR				1		1	2	
Blast clearance	1		1	1		1	4	
Resistant disease	1	1			1		3	

CR, complete remission; CRp, CR without platelet recovery; PR, partial remission.

Table 7. Response according to patient characteristics

Overall response (CR + CRp)	10/19 (52.6%)
Disease status	
Relapsed	8/13 (61.5%)
Refractory	2/6 (33.3%)
Cytogenetic group	
Favorable	1/2 (50.0%)
Intermediate	7/11 (53.6%)
Adverse	2/5 (40.0%)

CR, complete remission; CRp, CR without platelet recovery.

response tended to be higher in relapsed patients (61.4%) than in patients refractory to initial therapy (33.3%) (Table 7).

Discussion

As Kell et al.[19] suggested, the development of antibody-directed chemotherapy with more specificity against leukemic blasts has been one of the goals of cancer treatments for several years. CD33 antigen has emerged as a favored target epitope because it is expressed in over 80–90% of AML blasts.[22] Although unconjugated humanized anti-CD33 monoclonal antibodies has met with little success in relapsed disease, the antigen–antibody complex is rapidly internalized, suggesting that this would be a convenient drug delivery system to leukemia cells. GO is a humanized anti-CD33 monoclonal antibody conjugated to the extremely potent (toxic) antitumor drug calicheamicin. In the final report of a phase II trial in the USA and Europe, 277 patients were treated with standard doses of GO (9 mg/m^2, 2 h d.i.v. on days 1 and 15).[23] The response rate of younger patients was 27% (CR, 13%; CRp, 14%). Other clinical trials reported similar results with an approximate response rate of 26% (CR, 13%; CRp, 13%),[8,11,24] and the phase II part of the clinical trials in Japan resulted in a response rate of 30% (CR, 25%; CRp, 5%).[13]

As clinical efficacy of GO monotherapy for patients with relapsed or refractory AML has been limited, clinical studies are required for exploration of the role of GO in combination

therapy with conventional chemotherapy. Even though several groups in the USA and Europe have been evaluating the potential of GO already in different situations in the treatment of AML, the optimal usage of GO in combination therapy is still unknown, especially for Japanese patients. For this reason, we conducted the present study, starting from phase I, in order to evaluate the safety of GO-combined therapy.

As the final goal of our study is to investigate whether GO-combined therapy is meaningful for de novo adult AML (younger than age 65 years), we selected standard induction therapies, which are IDR 12 mg/m^2 on days 1–3 plus Ara-C 100 mg/m^2 on days 1–7, and DNR 50 mg/m^2 on days 1–5 plus Ara-C 100 mg/m^2 on days 1–7, as partner chemotherapeutic regimens.[4]

In the present study for relapsed or refractory AML, GO was administered on the next day after the final administration of anthracycline (IDR or DNR) with continuing administration of Ara-C.

As expected, grade 3/4 hematological toxicities and febrile neutropenia was observed in most patients, but those toxicities were clinically manageable. None of the patients died of adverse events, although one patient died of disease progression. The DLT (prolongation of neutropenia and thrombocytopenia, and serious infection [i.e. cerebral abscess]) were observed in all patients in level 3 of the IAG regimen (a dose of 5 mg/m^2 GO), but none in level 2 of the IAG regimen or level 3 of the DAG regimen. Therefore, the MTD of the IAG regimen was determined as level 2 (i.e. 3 mg/m^2 GO, 12 mg/m^2 IDR and 100 mg/m^2 Ara-C), and that of the DAG regimen as level 3 (i.e. 3 mg/m^2 GO, 50 mg/m^2 DNR and 100 mg/m^2 Ara-C).

Several attempts that combined the approved dosage of GO (9 mg/m^2, administered twice) with chemotherapy resulted in excess toxicity such as infection and liver toxicity, including increased risk of VOD/SOS.[25] The Cancer and Leukemia Group B (CALGB) 19902 study indicated that the dose schedule of 9 mg/m^2 GO on day 7 and 4.5 mg/m^2 GO on day 14 with high-dose Ara-C (3 g/m^2 per day for 5 days) caused a high rate of treatment-related death (four of the first seven patients, 57%).[18] In the present study, severe hepatotoxicity or VOD/

Table 8. Selected phase II trials of gemtuzumab ozogamicin (GO)-combining therapy for relapsed or refractory adult acute myeloid leukemia (AML)

Authors (name of regimen)	Institutes	No. patients	Median age (range) (years)	Combination of drugs	Dose and schedule of GO	% Response (CR/CRp)	Median OS (months)	Grade 3/4 non-hematological toxicity
Tsimberidou et al.[14] 2003 (MFAC)	MDACC	32	53 (18–78)	FLD: 15 mg/m² i.v. q12 h/day, days 2–4 Aa-C: 500 mg/m² 2 h d.i.v. q12 h/day, days 2–4 CSA: 6 mg/kg 2 h d.i.v. + 16 mg/kg c.i.v., days 1, 2	4.5 mg/m² 2 h d.i.v., day 1	34 (28/6)	5.3	Hyperbilirubinemia (18%), hepatic transaminitis (9%), VOD (3%)
Alvarado et al.[15] 2003 (MIA)	MDACC	14	61 (34–74)	IDR: 12 mg/m²/day i.v., days 2–4 Ara-C: 1.5 g/m²/day, days 2–5	6 mg/m² 2 h d.i.v., days 1, 15	42 (21/21)	2	Sepsis (71%), liver damage, VOD (14%)
Chevallier et al.[16] 2008 (MIDAM)	France	62	56 (16–71)	Ara-C: 1.5 g/m² 2 h d.i.v. q12 h/day, days 1–5 MIT: 12 mg/m²/day i.v., days 1–3	9 mg/m² 2 h d.i.v., day 4	63 (50/13)	9.5	Hyperbilirubinemia (16%), VOD (3%), early toxic death (6%)
Fianchi et al.[17] 2008 (G-Ara-My)	Italy	53	M	G-CSF: 5 µg/kg/day s.c., days 1–8 Ara-C: 100 mg/m²/day c.i.v., days 2–8 or 4–8	6 mg/m² 2 h d.i.v., day 9	45 (43/2)	9	Infection (36%), infusion reaction (5.5%), VOD (2%)
Stone et al.[18] 2010 (CALGB 19902)	CALGB	37	64 (55–70)	Ara-C: 3 g/m² 3 h d.i.v./day, days 1–5	9 mg/m² 2 h d.i.v., day 7	35 (32/3)	8.9	Hepatic transaminitis (29%), hyperbilirubinemia (27%), infection (92%), death of tox (8.1%)

Ara-C, cytarabine; CALGB, Cancer and Leukemia Group B; c.i.v., continuous venous infusion; CR, complete remission; CRp, CR without platelet recovery; CSA, cyclosporin A; d.i.v., drip venous infusion; FLD, fludarabine; G-CSF, granulocyte colony stimulating factor; IDR, idarubicin; iv, venous infusion; MDACC, MD Anderson Cancer Center; MIT, mitoxantrone; q12 h, every 12 h; OS, overall survival; VOD, veno-occlusive disease.

SOS was not observed in either of the IAG or DAG regimens, because we selected an initial dose of GO at 3 mg/m^2.

The MRC group already indicated in the AML15 prelude trial that a combination of 3 mg/m^2 but not 6 mg/m^2 of GO with intensive chemotherapy was safe and feasible for a multicenter trial in induction and consolidation therapy.[19] Our study confirmed a safe dose of GO as 3 mg/m^2, even though the timing of administration was different.

Although the present study was not designed to assess efficacy, it was of note that CR and CRp were achieved in nine (47.4%) and one (5.2%), respectively, out of 19 patients with relapsed or refractory AML. This overall rate of response, 52.6%, was comparable to the results of previous phase II trials for relapsed or refractory AML[14–18] (Table 8).

Clinical efficacy of the combination of GO with IDR + Ara-C (named MIA) was already evaluated by the MD Anderson Cancer Center.[15] Compared with our IAG regimen, the response rate of MIA (42%; CR, 21%; CRp, 21%) was quite similar, but their incidence of severe non-hematological toxicity was higher. Despite the fact that the doses of Ara-C and GO were lower in our IAG regimen, this combination will be feasible as an induction therapy for relapsed or refractory AML.

The MRC AML15 prelude trial[19] investigated safety and efficacy of GO in combination with DNR + Ara-C, in which DNR (50 mg/m^2 for 3 days) and Ara-C were combined with 3 mg/m^2 GO on day 1. Hematolopoietic recovery was satisfactory, and although two of eight enrolled patients developed grade 3 toxicity, all patients achieved CR and tolerated subsequent chemotherapy. In levels 2 and 3 of our DAG regimen, although the dose of DNR was higher than that of the MRC trial, the recovery from myelosuppression was satisfactory without excess of unexpected non-hematological toxicity.

During this phase I trial of GO in combination with chemotherapy for relapsed or refractory AML, several multicenter trials to investigate the role of GO combination for *de novo* AML have been completed in the USA and Europe. Burnett *et al.*[26] presented the results of the MRC AML15 trial, in which 1113 mostly younger, newly diagnosed patients with AML (except acute promyelocytic leukemia) were randomly assigned to one of three conventional induction therapies with or without 3 mg/m^2 GO on day 1. After achieving CR, 978 patients were randomly assigned to GO in combination with chemotherapy in course 3 of the consolidation therapy. The addition of GO was well tolerated with no significant increase in toxicity. Although there was no overall difference in response or survival, a predefined analysis by cytogenetic risk groups showed a significant survival benefit for patients with favorable risk and a trend for those with intermediate risk disease.

A similar study conducted by the Southwest Oncology Group (SWOG) was reported in abstract format.[27] In this SWOG 106 study, 627 patients with untreated AML (age 18–60 years) were randomly assigned to receive induction therapy either with Ara-C (100 mg/m^2 × 7 days) + DNR (60 mg/m^2 × 3 days) or with Ara-C (100 mg/m^2 × 7 days) + DNR (45 mg/m^2 × 3 days) + GO (6 mg/m^2). An interim analysis showed a CR rate of 66% in the GO-combined arm and 69% in the chemotherapy-alone arm (control arm), ruling out the originally hypothesized increase in CR of 12% by the addition of GO. There was no difference in disease-free survival (DFS) either, and the rate of fatal adverse events was higher in the GO-combined arm compared with the control arm (5.8% *vs* 0.8%). Based on these negative findings of the GO-combined arm, the FDA recommended to withdraw GO from the market in the USA.

However, as Burnett *et al.*[26] suggested, the SWOG 106 study is confounded, as the dose of DNR was lower in patients given GO, which might have masked any benefit of GO. In addition, the induction death rate in the GO arm was similar to what had been reported in other AML induction trials, but the mortality rate of the control arm was unexpectedly low. Nevertheless, in the SWOG study the benefit in the favorable subtype of AML was similarly observed in the MRC study.

Another smaller phase II study reported a high molecular response rate and DFS by GO in combination with high-dose Ara-C for core binding factor (CBF) leukemias.[28]

In conclusion, the present study demonstrated that 3 mg/m^2 of GO with IDR + Ara-C or DNR + Ara-C can be administered safely in younger adult patients with relapsed or refractory AML. As three clinical studies of GO-combined chemotherapy for newly diagnosed adult AML have indicated, there are subsets of AML, such as CBF leukemias, that could benefit from the addition of GO to conventional therapy. Intensive induction chemotherapy followed by a modest dose of GO like in our study protocol will be safely provided for salvage therapy regardless of cytogenetic risk groups. Fortunately, GO is still commercially available in Japan, therefore there is a need for confirmatory studies that investigate the efficacy of GO-combined chemotherapy for patients with AML as both initial and salvage therapy.

Disclosure Statement

The authors have no conflict of interest.

References

1 Acute myeloid leukemia in NCCN Clinical Guidelines in Oncology. [Cited 14 Jan 2011.] Available from URL: http://www.nccn.org/professionals/physician_gls/pdf/aml.pdf.

2 Fernandez HF, Sun Z, Yao X *et al.* Anthracycline dose intensification in acute myeloid leukemia. *N Engl J Med* 2009; **361**: 1249–59.

3 Lowenberg B, Ossenkoppele GJ, van Putten W *et al.* High-dose daunorubicin in older patients with acute myeloid leukema. *N Engl J Med* 2009; **361**: 1235–48.

4 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: JALSG AML201 Study. *Blood* 2011; **117**: 2358–65.

5 Wiernik PH, Banks PLC, 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**: 313–9.

6 Feldman EJ, Seiter K, Traganos F *et al.* Phase II evaluation of a high-dose mitoxantrone based induction regimen in untreated adults with acute myeloid leukemia. *Leuk Lymphoma* 2000; **38**: 309–15.

7 Estey EH. Treatment of relapsed and refractory acute myelogenous leukemia. *Leukemia* 2000; **14**: 476–9.

8 Sievers EL, Larson RA, Stadtmauer EA *et al.* Efficacy and safety of gemtuzumab ozogamicin in patients with CD33-positive acute myeloid leukemia in first relapse. *J Clin Oncol* 2001; **19**: 3244–54.

9 Larson RA. Current use and future development of gemtuzumab ozogamicin. *Semin Hematol* 2001; **38**: 24–31.

10 Van DerVelden VH, Te Marvelde JG, Hoogeveen PG *et al.* Targeting of the CD33-calicheamicin immunoconjugate Mylotarg (CMA-676) in acute myeloid leukemia: *in vivo* and *in vitro* saturation and internalization by leukemic and normal myeloid cells. *Blood* 2001; **97**: 3197–204.

11 Larson RA, Boogaerts M, Estey E *et al.* Antibody-targeted chemotherapy of older patients with acute myeloid leukemia in first relapse using Mylotarg (gemtuzumab ozogamicin). *Leukemia* 2002; **16**: 1627–36.

12 Bross PF, Beitz J, Chen G *et al.* Approval summary: gemtuzumab ozogamicin in relapsed acute myeloid leukemia. *Clin Cancer Res* 2001; **7**: 1490–6.

13 Kobayashi Y, Tobinai K, Takeshita A *et al.* Phase I/II study of humanized anti-CD33 antibody conjugated with calechiamicin, gemtuzumab ozogamicin, in relapsed or refractory acute myeloid leukemia: final results of Japanese multicenter cooperative study. *Int J Hematol* 2009; **89**: 460–9.

14 Tsimberidou A, Cortes J, Thomas D *et al.* Gemtuzumab ozogamicin, fludarabine, cytarabine and cyclosporine combination regimen in patients with CD33+ primary resistant or relapsed acute myeloid leukemia. *Leuk Res* 2003; **27**: 893–7.

15 Alvarado Y, Tsimberidou A, Kantarjian H *et al.* Pilot study of Mylotarg, idarubicin and cytarabine combination regimen in patients with primary resistant or relapsed acute myeloid leukemia. *Cancer Chemother Pharmacol* 2003; **51**: 87–90.

16 Chevallier P, Delaunay J, Turlure P *et al.* Long-term disease-free survival after gemtuzumab, intermediate-dose cytarabine, and mitoxantrone in patients with CD33+ primary resistant or relapsed acute myeloid leukemia. *J Clin Oncol* 2008; **26**: 5192–7.

17 Fianchi I, Pagano L, Leoni F *et al.* Gemtuzumab, cytarabine arabinoside, G-CSF combination (G-AraMy) in the treatment of elderly patients with poor-prognosis acute myeloid leukemia. *Ann Oncol* 2008; **19**: 128–34.

18 Stone RM, Moser B, Sanford B *et al.* High dose cytarabine plus gemtuzumab ozogamicin for patients with relapsed or refractory acute myeloid leukemia: Cancer and Leukemia Group B study 19902. *Leuk Res* 2011; **35**: 329–33.

19 Kell WJ, Burnett AK, Chopra R *et al.* A feasibility study of simultaneous administration of gemtuzumab ozogamicin with intensive chemotherapy in induction and consolidation in younger patients with acute myeloid leukemia. *Blood* 2003; **102**: 4277–83.

20 Grimwade D, Walker H, Oliver F *et al.* The importance of diagnostic cytogenetics on outcome in AML: analysis of 1,612 patients entered into the MRC AML 10 trial. *Blood* 1998; **92**: 2322–33.

21 Cheson BD, Bennett JM, Kopecky KJ *et al.* Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol* 2003; **21**: 4642–9.

22 Dinndorf PA, Andrews RG, Benjamin D *et al.* Expression of normal myeloid associated antigens by acute leukemia cells. *Blood* 1986; **67**: 1048–53.

23 Larson RA, Sievers EL, Stadtmauer EA *et al.* Final report of the efficacy and safety of gemtuzumab ozogamicin (Mylotarg) in patients with CD33-positive acute myeloid leukemia in first recurrence. *Cancer* 2005; **104**: 1442–52.

24 Piccaluga PP, Martinelli G, Rondoni M *et al.* Gemtuzumab ozogamicin for relapsed and refractory acute myeloid leukemia and myeloid sarcomas. *Leuk Lymphoma* 2004; **45**: 1791–5.

25 Tsimberidou AM, Giles FJ, Estey E *et al.* The role of gemtuzumab ozogamicin in acute leukaemia therapy. *Br J Haematol* 2006; **132**: 398–409.

26 Burnett AK, Hills RK, Milligan D *et al.* Identification of patients with acute myeloblastic leukemia who benefit from the addition of gemtuzumab ozogamicin: results of the MRC AML15 Trial. *J Clin Oncol* 2011; **29**: 369–77.

27 Petersdorf S, Kopecky K, Stuart RK *et al.* Preliminary results of Southwest Oncology Group Study S0106: an international intergroup phase 3 randomized trial comparing the addition of gemtuzumab ozogamicin to standard induction therapy versus standard unduction therapy followed by a second randomization to post-consolidation gemtuzumab ozogamicin versus no additional therapy for previously untreated acute myeloid leukemia. *Blood* (ASH Annual Meeting Abstracts) 2009; **114** (abs 790).

28 Borthakur G, Jappour E, Wang X *et al.* Effect of front-line therapy with fluradabine, cytarabine, filgrastim, and gemtuzumab ozogamicin (FLAG-GO) on outcome in core-binding factor associated acute myelogenous leukemia (CBF-AML). *J Clin Oncol* 2010; **28**: 466s (abs 6552).

blood

A randomized comparison of 4 courses of standard-dose multiagent chemotherapy versus 3 courses of high-dose cytarabine alone in postremission therapy for acute myeloid leukemia in adults: the JALSG AML201 Study

Shuichi Miyawaki, Shigeki Ohtake, Shin Fujisawa, Hitoshi Kiyoi, Katsuji Shinagawa, Noriko Usui, Toru Sakura, Koichi Miyamura, Chiaki Nakaseko, Yasushi Miyazaki, Atsushi Fujieda, Tadashi Nagai, Takahisa Yamane, Masafumi Taniwaki, Masatomo Takahashi, Fumiharu Yagasaki, Yukihiko Kimura, Norio Asou, Hisashi Sakamaki, Hiroshi Handa, Sumihisa Honda, Kazunori Ohnishi, Tomoki Naoe and Ryuzo Ohno

Updated information and services can be found at:
http://bloodjournal.hematologylibrary.org/content/117/8/2366.full.html

Articles on similar topics can be found in the following Blood collections
    Clinical Trials and Observations (3113 articles)
    Free Research Articles (1281 articles)
    Myeloid Neoplasia (605 articles)

Information about reproducing this article in parts or in its entirety may be found online at:
http://bloodjournal.hematologylibrary.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://bloodjournal.hematologylibrary.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://bloodjournal.hematologylibrary.org/site/subscriptions/index.xhtml

CLINICAL TRIALS AND OBSERVATIONS

A randomized comparison of 4 courses of standard-dose multiagent chemotherapy versus 3 courses of high-dose cytarabine alone in postremission therapy for acute myeloid leukemia in adults: the JALSG AML201 Study

Shuichi Miyawaki,[1] Shigeki Ohtake,[2] Shin Fujisawa,[3] Hitoshi Kiyoi,[4] Katsuji Shinagawa,[5] Noriko Usui,[6] Toru Sakura,[1] Koichi Miyamura,[7] Chiaki Nakaseko,[8] Yasushi Miyazaki,[9] Atsushi Fujieda,[10] Tadashi Nagai,[11] Takahisa Yamane,[12] Masafumi Taniwaki,[13] Masatomo Takahashi,[14] Fumiharu Yagasaki,[15] Yukihiko Kimura,[16] Norio Asou,[17] Hisashi Sakamaki,[18] Hiroshi Handa,[19] Sumihisa Honda,[20] Kazunori Ohnishi,[21] Tomoki Naoe,[4] and Ryuzo Ohno[22]

[1]Leukemia Research Center, Saiseikai Maebashi Hospital, Maebashi, Japan; [2]Department of Clinical Laboratory Science, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan; [3]Department of Hematology, Yokohama City University Medical Center, Yokohama, Japan; [4]Department of Hematology and Oncology, Nagoya University Graduate School of Medicine, Nagoya, Japan; [5]Hematology/Oncology Division, Okayama University Hospital, Okayama, Japan; [6]Division of Hematology and Oncology, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan; [7]Department of Internal Medicine, Japanese Red Cross Nagoya First Hospital, Nagoya, Japan; [8]Department of Hematology, Chiba University Hospital, Chiba, Japan; [9]Department of Hematology and Molecular Medicine Unit, Atomic Bomb Disease Institute, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan; [10]Department of Hematology and Oncology, Mie University Graduate School of Medicine, Tsu, Japan; [11]Division of Hematology, Jichi Medical University, Shimotsuke, Japan; [12]Department of Hematology, Osaka City University, Osaka, Japan; [13]Department of Clinical Molecular Genetics and Laboratory Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan; [14]Division of Hematology and Oncology, Department of Internal Medicine, St Marianna University School of Medicine, Kawasaki, Japan; [15]Department of Hematology, Saitama Medical School, Hidaka, Japan; [16]Division of Hematology, First Department of Internal Medicine, Tokyo Medical University, Tokyo, Japan; [17]Department of Hematology, Kumamoto University School of Medicine, Kumamoto, Japan; [18]Department of Hematology, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan; [19]Department of Medicine and Clinical Science, Gunma University Graduate School of Medicine, Maebashi, Japan; [20]Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan; [21]Oncology Center, Hamamatsu University School of Medicine, Hamamatsu, Japan; and [22]Aichi Cancer Center, Nagoya, Japan

We conducted a prospective randomized study to assess the optimal postremission therapy for adult acute myeloid leukemia in patients younger than 65 years in the first complete remission. A total of 781 patients in complete remission were randomly assigned to receive consolidation chemotherapy of either 3 courses of high-dose cytarabine (HiDAC, 2 g/m^2 twice daily for 5 days) alone or 4 courses of conventional standard-dose multiagent chemotherapy (CT) established in the previous JALSG AML97 study. Five-year disease-free survival was 43% for the HiDAC group and 39% for the multiagent CT group ($P = .724$), and 5-year overall survival was 58% and 56%, respectively ($P = .954$). Among the favorable cytogenetic risk group (n = 218), 5-year disease-free survival was 57% for HiDAC and 39% for multiagent CT ($P = .050$), and 5-year overall survival was 75% and 66%, respectively ($P = .174$). In the HiDAC group, the nadir of leukocyte counts was lower, and the duration of leukocyte less than 1.0×10^9/L longer, and the frequency of documented infections higher. The present study demonstrated that the multiagent CT regimen is as effective as our HiDAC regimen for consolidation. Our HiDAC regimen resulted in a beneficial effect on disease-free survival only in the favorable cytogenetic leukemia group. This trial was registered at www.umin.ac.jp/ctr/ as #C000000157. (Blood. 2011;117(8): 2366-2372)

Introduction

Approximately 70% to 80% of the newly diagnosed younger adult patients with acute myeloid leukemia (AML) achieve complete remission (CR) when treated with an anthracycline, usually daunorubicin (DNR) or idarubicin (IDR), and cytarabine (Ara-C); however, only approximately one-third of these patients remain free of disease for more than 5 years.[1-5] If CR patients are left untreated, almost all of them will relapse and die.[6] Therefore, postremission therapy is indispensable. Postremission therapy is divided into consolidation and maintenance therapy. In the previous studies of Japan Adult Leukemia Study Group (JALSG) for adult AML (AML87, 89, 92, and 95),[1-3,5] we administered 3 courses of consolidation therapy and 6 courses of intensified maintenance therapy. In the AML97 study,[7] we

conducted a randomized study to compare the conventional 3-course consolidation and 6-course maintenance therapies with 4 courses of intensive consolidation therapy without maintenance and demonstrated no difference in overall survival (OS) and disease-free survival (DFS). Therefore, the 4 courses of conventional standard-dose multiagent chemotherapy (CT) became the standard regimen in Japan. On the other hand, multiple cycles of high-dose cytarabine (HiDAC) have been commonly used as consolidation therapy in the United States and other countries. However, our national medical insurance system did not allow us to use HiDAC until 2001, and thus we could not use HiDAC in the previous treatment regimens for leukemia. We therefore conducted this prospective, multicenter cooperative

— 405 —
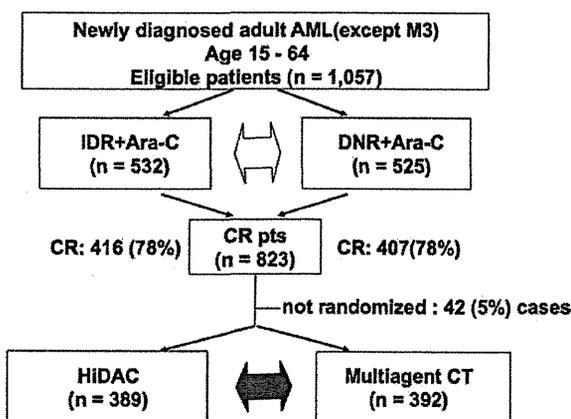
Figure 1. CONSORT diagram.

Table 1. Clinical characteristics of randomized patients

Characteristic	HiDAC (n = 389)	Multiagent CT (n = 392)	P
Age, y, median (range)	46 (15-64)	47 (15-64)	.697
WBC, ×10⁹/L, median (range)	15.6 (0.1-382)	14.9 (0.2-260)	.323
Karyotype, n			.210
Favorable	108	110	
Intermediate	242	256	
Adverse	27	14	
Unknown	12	12	
Induction, n			.914
IDR	196	196	
DNR	193	196	
Induction 1 cycle, %	81.0	81.4	.886

study to compare 4 courses of multiagent CT with 3 courses of HiDAC therapy after its approval in April 2001.

Methods

Patients

From December 2001 to December 2005, 1064 newly diagnosed adult patients 15 to 64 years of age with de novo AML were consecutively registered from 129 participating institutions. AML was first diagnosed by the French-American-British classification at each institution. Peripheral blood and bone marrow smears of registered patients were reevaluated by the central review committee. French-American-British M3 was not registered. Eligibility criteria included adequate function of liver (serum bilirubin < 2.0 mg/dL), kidney (serum creatinine < 2.0 mg/dL), heart and lung, and an Eastern Cooperative Oncology Group performance status between 0 and 3. Patients were not eligible if they had prediagnosed myelodysplastic syndrome or prior chemotherapy for other disorders. Cytogenetic abnormalities were grouped by standard criteria and classified according to the Medical Research Council classification.[8] The study was approved by institutional review boards at each participating institution. Written informed consent was obtained from all patients before registration in accordance with the Declaration of Helsinki.

Induction therapy consisted of Ara-C 100 mg/m^2 for 7 days and either IDR (12 mg/m^2 for 3 days) or DNR (50 mg/m^2 for 5 days). If patients did not achieve remission after the first course, the same therapy was administered once more. The outcome of induction therapy was reported to the JALSG Statistical Center before the consolidation therapy started. All CR patients were stratified according to induction regimen, number of courses of induction, age and karyotype, and randomized to receive either 4 courses of multiagent CT or 3 courses of HiDAC therapy. The first course

of multiagent CT consisted of mitoxantrone (7 mg/m^2 by 30-minute infusion for 3 days) and Ara-C (200 mg/m^2 by 24-hour continuous infusion for 5 days). The second consisted of DNR (50 mg/m^2 by 30-minute infusion for 3 days) and Ara-C (200 mg/m^2 by 24-hour continuous infusion for 5 days). The third consisted of aclarubicin (20 mg/m^2 by 30-minute infusion for 5 days) and Ara-C (200 mg/m^2 by 24-hour continuous infusion for 5 days). The fourth consisted of Ara-C (200 mg/m^2 by 24-hour continuous infusion for 5 days), etoposide (100 mg/m^2 by 1-hour infusion for 5 days), vincristine (0.8 mg/m^2 by bolus injection on day 8), and vindesine (2 mg/m^2 by bolus injection on day 10). Each consolidation was started as soon as possible after neutrophils, white blood cells (WBCs), and platelets recovered to more than 1.5 × 10⁹/L, 3.0 × 10⁹/L, and 100.0 × 10⁹/L, respectively. In the HiDAC group, 3 courses of Ara-C 2.0 g/m^2 by 3-hour infusion every 12 hours for 5 days were given. Each course was started 1 week after neutrophils, WBCs, and platelets recovered to the aforementioned counts.

Bone marrow examination was performed to confirm CR in both groups before each consolidation therapy and at the end of all consolidation therapy.

Best supportive care, including administration of antibiotics and platelet transfusions, was given if indicated. When patients had life-threatening documented infections during neutropenia, the use of granulocyte colony-stimulating factor was permitted.

After the completion of consolidation therapy, patients received no further chemotherapy. Allogeneic stem cell transplantation (allo-SCT) was offered during the first CR to patients of age 50 years or less with a histocompatible donor in the intermediate or adverse cytogenetic risk groups. Stem cell source was related donor or unrelated donor. Cord blood was not used. Conditioning before transplantation and prophylaxis for graft-versus-host disease were performed according to each institutional standard.

Responses were evaluated by the recommendations of the International Working Group.[9] CR was defined as the presence of all of the following: less than 5% of blasts in bone marrow, no leukemic blasts in peripheral blood, recovery of peripheral neutrophil counts more than 1.0 × 10⁹/L and platelet counts more than 100.0 × 10⁹/L, and no evidence of extramedullary leukemia. Relapse was defined as the presence of at least one of the
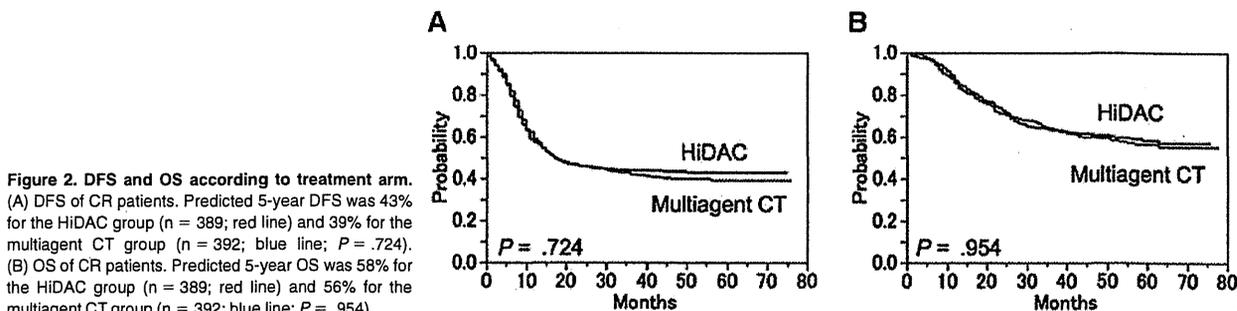

Figure 2. DFS and OS according to treatment arm. (A) DFS of CR patients. Predicted 5-year DFS was 43% for the HiDAC group (n = 389; red line) and 39% for the multiagent CT group (n = 392; blue line; P = .724). (B) OS of CR patients. Predicted 5-year OS was 58% for the HiDAC group (n = 389; red line) and 56% for the multiagent CT group (n = 392; blue line; P = .954).
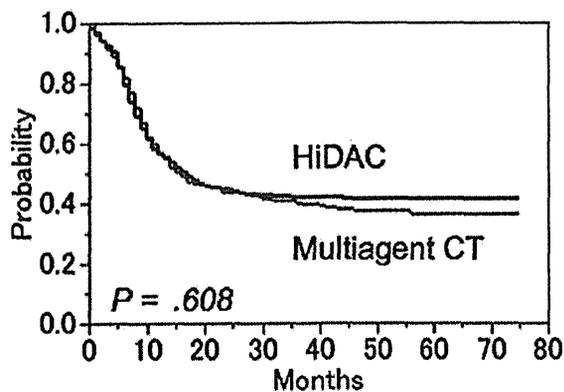
Figure 3. DFS according to treatment arm, after censoring the observation in transplanted patients. Predicted 5-year DFS was 41% for the HiDAC group (n = 389; red line) and 36% for the multiagent CT group (n = 392; blue line; P = .608).

following: reappearance of leukemic blasts in peripheral blood, recurrence of more than 5% blasts in bone marrow, and appearance of extramedullary leukemia.

Statistical analysis

This was a multi-institutional randomized phase 3 study with a 2 × 2 factorial design. The primary endpoint of the first randomization was CR rate, and a sample size of 420 patients per group was estimated to have a power of 90% at a 1% level of significance to demonstrate noninferiority (assuming 80% CR rate for both groups). For the second randomization (ie, this study), the primary endpoint was DFS, and the secondary end points were OS and adverse events of grade 3 or more by National Cancer Institute Common Toxicity Criteria. A sample size of 280 patients per group was estimated to have a power of 80% at a 5% level of significance to 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 test. The Wilcoxon rank-sum test was used for continuous data, such as age and WBC count, whereas the χ^2 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) and R software Version 2.9.1 (www.r-project.org).

Results

Response to induction therapy

Of 1064 patients registered, 1057 patients were evaluable. Seven patients (1 misdiagnosis, 1 infectious complication, 1 without therapy, and 4 withdrawal of consent) were excluded. Median age was 47 years (range, 15-64 years). Cytogenetic studies were performed in 99.2% of registered patients and the results were available in 97%. Of 1057 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% vs 77.5%). Percentage of patients who reached CR after the first induction course was also similar (64.1% vs 61.1%, P = .321). Day to achieve CR was longer in the IDR arm than the DNR arm (33.8 vs 32.4 days, P = .038). The detailed result of induction phase of this study is reported in a separate paper.[10]

Postremission 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). The remaining 781 patients were randomly assigned to receive either the HiDAC regimen (389) or the multiagent CT regimen (392; Figure 1). Clinical characteristics of 2 treatment groups were well balanced in age, initial WBC count, cytogenetic risk, induction arm, and induction cycle (Table 1).

DFS and OS

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 = .724; Figure 2A). Five-year OS was 58% for the HiDAC group and 56% for the multiagent CT group (P = .954; Figure 2B). 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 = .608; Figure 3).

The cumulative incidences of relapse and treatment-related mortality during CR, respectively, were 49% and 8% for the HiDAC group and 56% and 5% for the multiagent CT group (P = .294, P = .172; Figure 4A). 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 = .402, P = .409), respectively (Figure 4B).
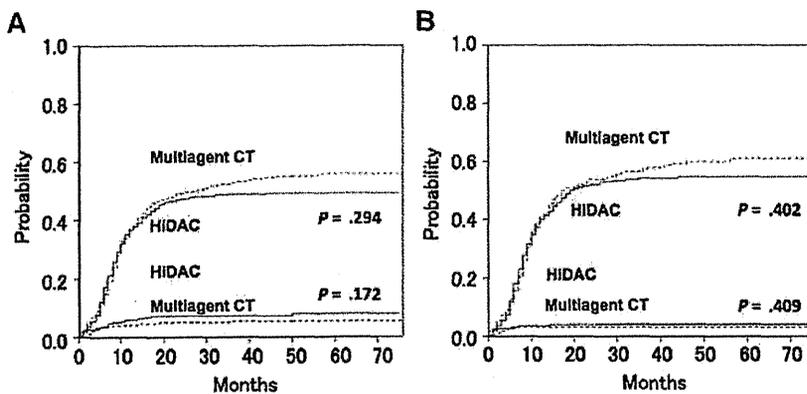
A

B

Figure 4. Cumulative incidence of relapse and treatment-related mortality in CR by treatment arm. (A) The incidences of relapse and mortality, respectively, were 49% and 8% for the HiDAC group (solid line) and 56% and 5% for the multiagent CT group (dotted line; P = .324, P = .172). (B) After censoring the observation in transplanted patients, the incidences of relapse and mortality, respectively, were 55% and 4% for the HiDAC group (solid line) and 61% and 3% for the multiagent CT group (dotted line; P = .402, P = .409).

Figure 5. DFS and OS 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 = .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 = .174).
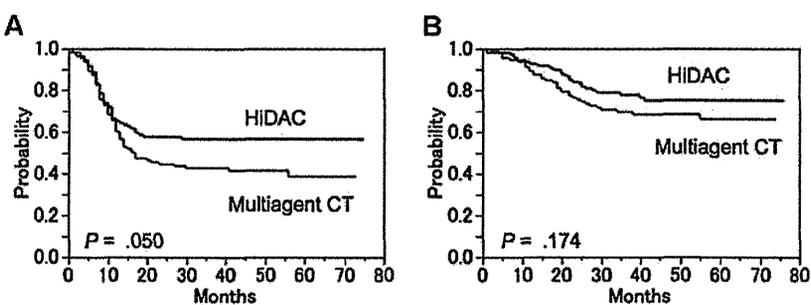
In patients with the favorable cytogenetics, core-binding factor (CBF) leukemia with t(8;21) or inv(16), 5-year DFS was 57% in the HiDAC group and 39% in the multiagent CT group (P = .050; Figure 5A), and 5-year OS was 75% and 66%, respectively (P = .174; Figure 5B).

In patients with the intermediate cytogenetics, 5-year DFS was 38% in the HiDAC group and 39% in the multiagent CT group (P = .403; Figure 6A), and 5-year OS was 53% and 54%, respectively (P = .482; Figure 6B). In patients with the adverse cytogenetics, 5-year DFS was 33% in the HiDAC group and 14% in the multiagent CT group (P = .364; Figure 7A), and 5-year OS was 39% and 21%, respectively (P = .379; Figure 7B). Among younger patients ($\leq$ 50 years), 5-year DFS was 45% in the HiDAC group and 46% in the multiagent CT group (P = .590), and 5-year OS was 62% and 66%, respectively (P = .228). Among the older patients (> 50 years), 5-year DFS was 40% in the HiDAC group and 28% in the multiagent CT group (P = .230), and 5-year OS was 51% and 40%, respectively (P = .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 = .641), and 5-year OS was 58% and 57%, respectively (P = .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 = .339), and 5-year OS was 58% and 56%, respectively (P = .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 × 10⁹/L, the number of induction therapies, and age more than 50 years, and for OS, age more than 50 years, the number of induction therapies, WBC more than 20 × 10⁹/L, and myeloperoxidase-positive blast less than 50%. Induction therapy, consolidation therapy, and cytogenetic risk group were not independent prognostic factors for DFS or OS by this multivariate analysis (Table 2).

Tolerance and toxicity of postremission 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 first 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 less than 1.0 × 10⁹/L. After each course of consolidation, the nadir of WBC count was significantly lower (P < .0001) and the day of WBC less than 1.0 × 10⁹/L was significantly longer in the HiDAC group (P < .001). During each course of consolidation, the frequency and the number of days of granulocyte colony-stimulating factor administration were significantly higher in the HiDAC group. Table 5 shows toxic adverse events, excluding hematologic side effects. The frequency of documented infections was significantly higher in the HiDAC group (P < .001). The subset analysis showed the high incidence of documented infection in HiDAC regimen only in intermediate cytogenetic risk group (P < .001).

Discussion

To determine the best postremission therapy, there have been several prospective randomized studies comparing chemotherapy
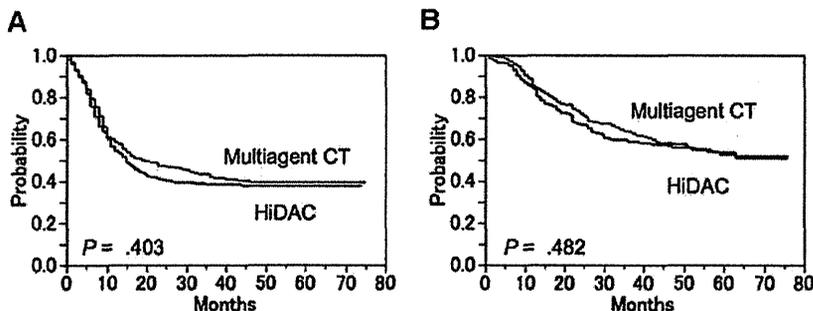

Figure 6. DFS and OS by treatment arm for the intermediate cytogenetic risk group. (A) Predicted 5-year DFS was 38% for the HiDAC group (n = 242; red line) and 39% for the multiagent CT group (n = 256; blue line; P = .403). (B) Predicted 5-year OS was 53% for the HiDAC group (n = 242; red line) and 54% for the multiagent CT group (n = 256; blue line; P = .482).
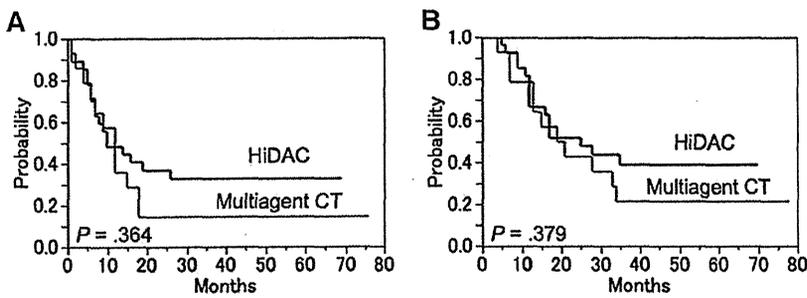
Figure 7. DFS and OS by treatment arm for the adverse cytogenetic risk group. (A) Predicted 5-year DFS was 33% for the HiDAC group (n = 27; red line) and 14% for the multiagent CT group (n = 14; blue line; P = .364). (B) Predicted 5-year OS was 39% for the HiDAC group (n = 27; red line) and 21% for the multiagent CT group (n = 14; blue line; P = .379).

with SCT. Although there is some limitation in SCT, such as patient age and availability of human leukocyte antigen–identical donors, most randomized studies demonstrate that SCT, the most intensive postremission modality, provides superior or at least noninferior prognosis in high- or intermediate-risk adult AML.[11-13]

As for postremission chemotherapy, HiDAC therapy is generally used in the United States and other countries after the landmark Cancer and Leukemia Group B-8525 (CALGB-8525) study.[14] In Japan, however, because 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 resulting from more severe and longer-lasting neutropenia. In the CALGB-8525 study,[14] patients randomized to 4 cycles of HiDAC regimen were administered 3 g/m² of Ara-C by 3-hour infusion, twice daily on days 1, 3, and 5, and our patients randomized to 3 cycles of HiDAC regimen were given 2 g/m² 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/m² vs 60 g/m²). The Acute Leukemia French Association Group compared a timed-sequential consolidation consisting of etoposide, mitoxantrone, and Ara-C with a postremission chemotherapy, including 4 cycles of HiDAC (3 g/m²), and reported that there were no statistically significant differences between the 2 groups in the rates of event-free survival and OS at 3 years.[15] The British Medical Research Council also compared a conventional Medical Research Council schedule (MACE/MidAC) with 2 courses of

HiDAC regimens (3 g/m² or 1.5 g/m²) 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/m² for 5 days) or to the conventional dose of Ara-C (100 mg/m² 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. Indeed, the CALGB-9222 study[17] showed no difference in DFS and OS between the HiDAC group and the intensified sequential multiagent 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 the HiDAC group (n = 108) tended to be superior to that of the multiagent CT group (n = 110) in DFS (57% vs 39%; P = .050) and OS (75% vs 66%; P = .174) but not at statistically significant level; and in the adverse risk group, the similar but statistically nonsignificant trend in DFS (33% vs 14%) and OS (39% vs 21%) was noted. Bloomfield et al[19] reported that the 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 the HiDAC regimen. However, our study showed that DFS of CBF leukemia (n = 108) treated with the HiDAC regimen was only 57% at 5 years.

There are 2 possible explanations of difference between our results and those reported by Bloomfield et al.[19] One is that their superior results may come from a small number of patients (n = 18). Indeed, 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 have KIT mutations, which confer

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

Survival type/variable	Category	Hazard ratio	P
DFS			
Initial WBC count	≥ 20 × 10⁹/L	1.49	< .0001
No. of induction therapies	2 courses	1.50	.0006
Age, y	> 50	1.33	.0028
Consolidation therapy	Multiagent CT	1.04	.7128
OS			
Age, y	> 50	2.00	< .0001
No. of induction therapies	2 courses	1.58	.0033
Initial WBC count	≥ 20 × 10⁹/L	1.41	.0070
MPO-positive blast	< 50 %	1.42	.0149
Consolidation therapy	Multiagent CT	0.96	.7768

MPO indicates myeloperoxidase.

Table 3. Tolerance of consolidation

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

*P < .05.

Table 4. Intensity of consolidation

	HiDAC	Multiagent CT	P
After first consolidation			
Lowest WBC, ×10⁹/L	0.17	0.40	< .0001
Days WBC < 1.0 × 10⁹/L	13 (0-40)	12 (0-36)	.0005
After second consolidation			
Lowest WBC, ×10⁹/L	0.10	0.40	< .0001
Days WBC < 1.0 × 10⁹/L	14 (0-34)	13 (0-241)	.0007
After third consolidation			
Lowest WBC, ×10⁹/L	0.10	0.40	< .0001
Days WBC < 1.0 × 10⁹/L	14 (0-38)	11.5 (0-28)	< .0001
After fourth consolidation			
Lowest WBC, ×10⁹/L		0.40	
Days WBC < 1.0 × 10⁹/L		12 (0-34)	

Values are median (range).

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, a 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. The small number of this cohort may explain the statistical insignificance. Nevertheless, HiDAC therapy may be recommended to this group if patients have no human leukocyte antigen–matched donor.

Recently, IDR is frequently included into induction regimen for AML because of its better effectiveness compared with DNR.[24-26] A meta-analysis of randomized trials showed that the use of IDR instead of DNR results in a high CR rate.[27] However, a German group reported that the advantage of IDR in response rate may be

Table 5. Adverse events (CTC grades 3 and 4) during consolidation therapy

	HiDAC, %	Multiagent CT, %	P
Documented infection	20.9	14.5	< .001
Febrile neutropenia	66.5	66.4	.311
Bleeding	0.8	0.7	.601
Early death*	0.9	0.6	.389

*Death within 30 days after consolidation chemotherapy.

lost during HiDAC consolidation therapy because of 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 2 courses of the IDR regimen were given before the HiDAC consolidation, only 19% of patients required 2 courses to obtain CR. In contrast, the German group gave 2 courses of IDR induction regimen before the HiDAC consolidation. Thus, severe adverse events during HiDAC therapy probably 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.

In conclusion, postremission consolidation regimen should be selected on the basis of prognostic factors, such as cytogenetics. Although several types of HiDAC regimen have been widely adopted as the optimal postremission 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.

Authorship

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

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Shuichi Miyawaki, Division of Hematology, Tokyo Metropolitan Ohtsuka Hospital, 2-8-1 Minamiohtsuka, Toshima-ku, Tokyo, 170-8476, Japan; e-mail: miyawaki@ mail.wind.ne.jp.

References

1. Ohno R, Kobayashi T, Tanimoto M, et al. Randomized study of individualized induction therapy with or without vincristine, and of maintenance-intensification therapy between 4 or 12 courses in adult acute myeloid leukemia: AML-87 Study of the Japan Adult Leukemia Study Group. Cancer. 1993;71(12):3888-3895.

2. Kobayashi T, Miyawaki S, Tanimoto M, et al. Randomized trials between behenoyl cytarabine and cytarabine in combination induction and consolidation therapy, and with or without ubenimex after maintenance/intensification therapy in adult acute myeloid leukemia. J Clin Oncol. 1996;14(1):204-213.

3. Miyawaki S, Tanimoto M, Kobayashi T, et al. No beneficial effect from addition of etoposide to

daunorubicin, cytarabine, and 6-mercaptopurine in individualized induction therapy of adult acute myeloid leukemia: the JALSG-AML92 study. Int J Hematol. 1999;70(2):97-104.

4. Büchner T, Hiddemann W, Berdel WE, et al. 6-Thioguanine, cytarabine, and daunorubicin (TAD) and high-dose cytarabine and mitoxantrone (HAM) for induction, TAD for consolidation, and either prolonged maintenance by reduced monthly TAD or TAD-HAM-TAD and one course of intensive consolidation by sequential HAM in adult patients at all ages with de novo acute myeloid leukemia (AML): a randomized trial of the German AML Cooperative Group. J Clin Oncol. 2003;21(24):4496-4504.

5. Ohtake S, Miyawaki S, Kiyoi H, et al. Random-

ized trial of response-oriented individualized versus fixed-schedule induction chemotherapy with idarubicin and cytarabine in adult acute myeloid leukemia: the JALSG AML95 study. Int J Hematol. 2010;91(2):276-283.

6. Cassileth PA, Harrington DP, Hines JD, et al. Maintenance chemotherapy prolongs remission duration in adult acute nonlymphocytic leukemia. J Clin Oncol. 1988;6(4):583-587.

7. Miyawaki S, Sakamaki H, Ohtake S, et al. A randomized, postremission comparison of four courses of standard-dose consolidation therapy without maintenance therapy versus three courses of standard-dose consolidation with maintenance therapy in adults with acute myeloid leukemia. Cancer. 2005;104(12):2726-2734.

8. Grimwade D, Walker H, Oliver F, et al. The importance of diagnostic cytogenetics on outcome in AML: analysis of 1612 patients entered into the MRC AML 10 trial. *Blood.* 1998;92(7):2322-2333.

9. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol.* 2003; 21(24):4642-4649.

10. 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: JALSG AML201 Study. *Blood.* 2011;117(8):2357-2364.

11. Zittoun RA, Mandelli F, Willemze R, et al. Autologous or allogeneic bone marrow transplantation compared with intensive chemotherapy in acute myeloid leukemia. *N Engl J Med.* 1995;332(4): 217-223.

12. Burnett AK, Wheatley K, Goldstone AH et al. The value of allogeneic bone marrow transplant in patients with acute myeloid leukaemia at differing risk of relapse: results of the UK MRC AML 10 trial. *Br J Haematol.* 2002;118(2):385-400.

13. Sakamaki H, Miyawaki S, Ohtake S, et al. Allogeneic stem cell transplantation versus chemotherapy as post-remission therapy for intermediate or poor risk adult acute myeloid leukemia: results of the JALSG AML97 study. *Int J Hematol.* 2010;91(2):284-292.

14. Mayer RJ, Davis RB, Schiffer CA, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. *N Engl J Med.* 1994;331(14): 896-903.

15. Thomas X, Raffoux E, Botton S et al. Effect of priming with granulocyte-macrophage colony-stimulating factor in younger adults with newly diagnosed acute myeloid leukemia: a trial by the Acute Leukemia French Association (ALFA) Group. *Leukemia.* 2007;21(3):453-461.

16. Burnett AK, Hills RK, Milligan D, et al. Attempts to optimise induction and consolidation chemotherapy in patients with acute myeloid leukaemia: results of the MRC AML15 trial [abstract]. *Blood.* 2009;114(22):200. Abstract 484

17. Moore JO, George SL, Dodge RK, et al. Sequential multiagent chemotherapy is not superior to high-dose cytarabine alone as postremission intensification therapy for acute myeloid leukemia in adults under 60 years of age: Cancer and Leukemia group B study 9222. *Blood.* 2005;105(9): 3420-3427.

18. Slovak ML, Kopecky KJ, Cassileth PA et al. Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: a Southwest Oncology Group/Eastern Cooperative Oncology Group study. *Blood.* 2000;96(13):4075-4083.

19. Bloomfield CD, Lawrence D, Byrd JC, et al. Frequency of prolonged remission duration after high-dose cytarabine intensification in acute myeloid leukemia varies by cytogenetic subtype. *Cancer Res.* 1998;58(18):4173-4179.

20. Paschka P, Marcucci G, Ruppert AS, et al. Adverse prognostic significance of KIT mutations in adult acute myeloid leukemia with inv(16) and t(8;21): a Cancer and Leukemia Group B Study. *J Clin Oncol.* 2006;24(24):3904-3911.

21. Cairoli R, Beghini A, Grillo G, et al. Prognostic impact of c-KIT mutations in core binding factor leukemias: an Italian retrospective study. *Blood.* 2006;107(9):3463-3468.

22. Nanri T, Matsuno N, Kawakita T, et al. Mutations in the receptor tyrosine kinase pathway are associated with clinical outcome in patients with acute myeloblastic leukemia harboring t(8;21)(q22; q22). *Leukemia.* 2005;19(8):1361-1366.

23. Wang YY, Zhou GB, Yin T, et al. AML1-ETO and C-KIT mutation/overexpression in t(8;21) leukemia: implication in stepwise leukemogenesis and response to Gleevec. *Proc Natl Acad Sci U S A.* 2005;102(4):1104-1109.

24. 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(8):1666-1674.

25. 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(2):313-319.

26. Vogler WR, Velez-Garcia E, Weiner RS, et al. A phase III trial comparing idarubicin and daunorubicin in combination with cytarabine in acute myelogenous leukemia: a Southeastern Cancer Study Group Study. *J Clin Oncol.* 1992;10(7): 1103-1111.

27. AML Collaborative Group. A systematic collaborative overview of randomized trials comparing idarubicin with daunorubicin (or other anthracyclines) as induction therapy for acute myeloid leukaemia. *Br J Haematol.* 1998;103(1):100-109.

28. Seipelt G, Hofmann WK, Martin H, et al. Comparison of toxicity and outcome in patients with acute myeloid leukemia treated with high-dose cytosine arabinoside consolidation after induction with a regimen containing idarubicin or daunorubicin. *Ann Hematol.* 1998;76(3):145-151.

blood

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

Shigeki Ohtake, Shuichi Miyawaki, Hiroyuki Fujita, Hitoshi Kiyoi, Katsuji Shinagawa, Noriko Usui, Hirokazu Okumura, Koichi Miyamura, Chiaki Nakaseko, Yasushi Miyazaki, Atsushi Fujieda, Tadashi Nagai, Takahisa Yamane, Masafumi Taniwaki, Masatomo Takahashi, Fumiharu Yagasaki, Yukihiko Kimura, Norio Asou, Hisashi Sakamaki, Hiroshi Handa, Sumihisa Honda, Kazunori Ohnishi, Tomoki Naoe and Ryuzo Ohno

---

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

Shigeki Ohtake,[1] Shuichi Miyawaki,[2] Hiroyuki Fujita,[3] Hitoshi Kiyoi,[4] Katsuji Shinagawa,[5] Noriko Usui,[6] Hirokazu Okumura,[7] Koichi Miyamura,[8] Chiaki Nakaseko,[9] Yasushi Miyazaki,[10] Atsushi Fujieda,[11] Tadashi Nagai,[12] Takahisa Yamane,[13] Masafumi Taniwaki,[14] Masatomo Takahashi,[15] Fumiharu Yagasaki,[16] Yukihiko Kimura,[17] Norio Asou,[18] Hisashi Sakamaki,[19] Hiroshi Handa,[20] Sumihisa Honda,[21] Kazunori Ohnishi,[22] Tomoki Naoe,[4] and Ryuzo Ohno[23]

[1]Department of Clinical Laboratory Science, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan; [2]Leukemia Research Center, Saiseikai Maebashi Hospital, Maebashi, Japan; [3]Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, Yokohama, Japan; [4]Department of Hematology and Oncology, Nagoya University Graduate School of Medicine, Nagoya, Japan; [5]Hematology/Oncology Division, Okayama University Hospital, Okayama, Japan; [6]Division of Hematology and Oncology, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan; [7]Department of Hematology, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan; [8]Department of Internal Medicine, Japanese Red Cross Nagoya First Hospital, Nagoya, Japan; [9]Department of Hematology, Chiba University Hospital, Chiba, Japan; [10]Department of Hematology and Molecular Medicine Unit, Atomic Bomb Disease Institute, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan; [11]Department of Hematology and Oncology, Mie University Graduate School of Medicine, Tsu, Japan; [12]Division of Hematology, Jichi Medical University, Shimotsuke, Japan; [13]Department of Hematology, Osaka City University, Osaka, Japan; [14]Department of Clinical Molecular Genetics and Laboratory Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan; [15]Division of Hematology and Oncology, Department of Internal Medicine, St Marianna University School of Medicine, Kawasaki, Japan; [16]Department of Hematology, Saitama Medical School, Hidaka, Japan; [17]Division of Hematology, First Department of Internal Medicine, Tokyo Medical University, Tokyo, Japan; [18]Department of Hematology, Kumamoto University School of Medicine, Kumamoto, Japan; [19]Department of Hematology, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan; [20]Department of Medicine and Clinical Science, Gunma University Graduate School of Medicine, Maebashi, Japan; [21]Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan; [22]Oncology Center, Hamamatsu University School of Medicine, Hamamatsu, Japan; and [23]Aichi Cancer Center, Nagoya, Japan

We conducted a multi-institutional randomized study to determine whether high-dose daunorubicin would be as effective as standard-dose idarubicin in remission-induction therapy for newly diagnosed adult patients younger than 65 years of age with acute myeloid leukemia. Of 1064 patients registered, 1057 were evaluable. They were randomly assigned to receive either daunorubicin (50 mg/m^2 daily for 5 days) or idarubicin (12 mg/m^2 daily for 3 days) in combination with 100 mg/m^2 of cytarabine by continuous infusion daily for 7 days as induction therapy. Complete remission was achieved in 407 (77.5%) of 525 patients in the daunorubicin group and 416 (78.2%) of 532 in the idarubicin group ($P = .79$). Patients achieving complete remission received intensive postremission therapy that consisted of either 3 courses of high-dose cytarabine or 4 courses of standard-dose therapy. Overall survival rates at 5 years were 48% for the daunorubicin group and 48% for the idarubicin group ($P = .54$), and relapse-free survival rates at 5 years were 41% and 41% ($P = .97$), respectively. Thus, high-dose daunorubicin and standard-dose idarubicin were equally effective for the treatment of adult acute myeloid leukemia, achieving a high rate of complete remission and good long-term efficacy. This study is registered at http://www.umin.ac.jp/ctrj/ as C000000157. (*Blood.* 2011;117(8): 2358-2365)

Introduction

The combination of anthracycline and cytarabine (Ara-C) with or without other antileukemia drugs is a standard induction therapy for acute myeloid leukemia (AML),[1-3] and a combination of daunorubicin at a dose of 45 to 50 mg/m^2 given daily for 3 days and Ara-C at a dose of 100 to 200 mg/m^2 given daily for 7 days generally has been used. In the late 1980s, however, idarubicin was introduced into clinics, and 3 randomized studies comparing idarubicin with daunorubicin reported significantly higher complete remission (CR) rates in favor of idarubicin.[4-6] A meta-analysis also confirmed a superior effect of idarubicin at a dose of 10 to 12 mg/m^2 for 3 days versus daunorubicin at a dose of 45 to 60 mg/m^2 for 3 days in the achievement of CR.[7] Nevertheless, the long-term follow-up of the above-mentioned 3 randomized studies comparing idarubicin with daunorubicin revealed that the idarubicin group had better overall survival (OS) than the daunorubicin group in only 1 study.[8]

The Japan Adult Leukemia Study Group (JALSG) used idarubicin and Ara-C as induction therapy in the AML95 and AML97 studies,[9-11] after idarubicin was registered and approved for the national health insurance system in 1995. Both studies resulted in satisfactorily high CR rates (80% and 79%, respectively); however, these CR rates were not superior to those of our earlier AML87, AML89, and AML92 studies, which used daunorubicin in combination with other antileukemia drugs.[12-14] In these 3 previous studies,

---

daunorubicin and other drugs were administered in a response-oriented individualized manner; that is, additional drugs were given for a few days when the bone marrow at day 8 was not hypoplastic, containing a substantial number of blasts. Therefore, the total doses of daunorubicin administered during the first course of induction therapy were 240 to 280 mg/m² given for more than 5 to 7 days, which was more than the conventional dose of 40 to 60 mg/m² given for 3 days. Usui et al also reported that the optimal dose of daunorubicin in their induction therapy for newly diagnosed adult AML was approximately 280 mg/m² (40 mg/m² for 7 days).[15]

Because there had been no prospective randomized study comparing a higher dose of daunorubicin with the standard dose of idarubicin (12 mg/m²) in adult AML, in the present multi-institutional randomized study, we prospectively compared idarubicin (12 mg/m² for 3 days) with daunorubicin (50 mg/m² for 5 days), in combination with Ara-C (100 mg/m² for 7 days), as induction therapy for previously untreated adult AML. High-dose daunorubicin resulted in the same CR rate and predicted 5-year OS compared with standard-dose idarubicin.

Methods

Patients

From December 2001 to December 2005, 1064 newly diagnosed adult patients 15 to 64 years of age with de novo AML were consecutively registered from 129 participating institutions. AML was first diagnosed by the French-American-British (FAB) classification at each institution. Peripheral blood and bone marrow smears from all registered patients were sent to Nagasaki University and examined by May-Giemsa, peroxidase, and esterase staining. Next, diagnosis was reevaluated by the central review committee. Patients with the FAB M3 subtype were not registered in the present study. Eligibility criteria included adequate function of liver (serum bilirubin level < 2.0 mg/dL), kidney (serum creatinine < 2.0 mg/dL), heart, and lung and an Eastern Cooperative Oncology Group performance status between 0 and 3. Patients were not eligible if they had prediagnosed myelodysplastic syndrome, but they were eligible if they had no definite diagnosis of myelodysplastic syndrome confirmed by bone marrow histologic analysis even when they had a previous history of hematologic abnormality. Cytogenetic abnormalities were grouped by standard criteria and classified according to the Medical Research Council classification.[16] The study was approved by the institutional review boards at each participating institution. Written informed consent was obtained from all patients before registration in accordance with the Declaration of Helsinki. The study was registered at http://www.umin.ac.jp/ctr/ as C000000157.

Treatments

Patients were randomly assigned by use of a centralized computer system to receive either idarubicin or daunorubicin. Randomization was stratified by age (younger or older than 50 years) and type of AML (FAB classification). All patients received 100 mg/m²/d Ara-C by 24-hour continuous infusion from days 1 to 7. In the idarubicin group, patients received 12 mg/m²/d idarubicin for 3 days, and in the daunorubicin group, they received 50 mg/m²/d daunorubicin for 5 days. If patients did not achieve CR by the first course, the same induction therapy was repeated after an approximately 3- to 4-week interval. If patients did not achieve CR with 2 courses, they were judged as failure cases.

All patients who achieved CR were again randomized to receive either 4 courses of conventional consolidation therapy or 3 courses of high-dose Ara-C therapy. In the conventional consolidation-therapy group, the first course consisted of mitoxantrone (7 mg/m² by 30-minute infusion on days 1 to 3) and Ara-C (200 mg/m² by 24-hour continuous infusion on days 1 to

5). The second course consisted of daunorubicin (50 mg/m² by 30-minute infusion on days 1 to 3) and Ara-C (200 mg/m² by 24-hour continuous infusion on days 1 to 5). The third course consisted of aclarubicin (20 mg/m² by 30-minute infusion on days 1 to 5) and Ara-C (200 mg/m² by 24-hour continuous infusion on days 1 to 5). The fourth course consisted of Ara-C (200 mg/m² by 24-hour continuous infusion on days 1 to 5), etoposide (100 mg/m² by 1-hour infusion on days 1 to 5), vincristine (0.8 mg/m² by bolus injection on day 8), and vindesine (2 mg/m² by bolus injection on day 10). Each consolidation was administered as soon as possible after the neutrophils, white blood cells (WBCs), and platelets recovered to more than 1.5 × 10⁹/L, 3.0 × 10⁹/L, and 100 × 10⁹/L, respectively. In the high-dose Ara-C group, 3 courses of 2.0 g/m² Ara-C were given by 3-hour infusion every 12 hours on days 1 to 5. Each course was administered 1 week after the neutrophils, WBCs, and platelets recovered to the above counts.

The best supportive care, including administration of antibiotics and platelet transfusions, was given as indicated. When patients had life-threatening documented infections during neutropenia, the use of granulocyte colony-stimulating factor was permitted.

After completion of consolidation therapy, no patients received further chemotherapy. Allogeneic stem cell transplantation (SCT) was offered during the first CR to patients 50 years of age or younger and with a histocompatible donor in the intermediate or adverse cytogenetic risk groups.

Definitions and study end points

Responses were evaluated according to the recommendations of the International Working Group.[17] CR was defined as the presence of all of the following: fewer than 5% blasts in bone marrow, no leukemic blasts in peripheral blood, recovery of peripheral neutrophil counts to more than 1.0 × 10⁹/L and platelet counts to more than 100 × 10⁹/L, and no evidence of extramedullary leukemia. Relapse after CR was defined as the presence of at least 1 of the following: reappearance of leukemic blasts in the peripheral blood, recurrence of more than 5% blasts in the bone marrow not attributable to any other cause (eg, bone marrow regeneration after consolidation therapy), and appearance of extramedullary leukemia.

This was a multi-institutional, randomized, phase 3 study with a 2 × 2 factorial design. The primary end point of the first randomization was CR rate. The result of the second randomization is reported here in part but will be presented fully in a separate paper. OS was calculated from the date of entry into the study until death due to any cause and was censored at the last follow-up. Relapse-free survival (RFS) for patients who achieved CR was measured from the date of CR until the date of AML relapse or death of any cause and was censored at the last follow-up. Patients who underwent allogeneic SCT were not censored at the date of SCT.

Statistical analysis

This study was prospectively powered to demonstrate noninferiority of daunorubicin compared with idarubicin. With a sample size of 420 patients per group (840 in total), the study had a power of 90% at a 1% level of significance to demonstrate noninferiority (assuming an 80% CR rate for both groups). Statistical testing for the noninferiority trial was performed according to the method of Blackwelder.[18] The Kaplan-Meier method was used to estimate probabilities of OS and RFS.[19] To test factors that predict CR, the χ^2 test and Wilcoxon rank sum test were used for univariate analysis, and the multiple logistic regression model was used for multivariate analysis. For comparison of OS and RFS, the log-rank test was used for univariate analysis and the proportional hazard model of Cox for multivariate analysis.[20,21] Cumulative rates of CR, neutrophil recovery, and platelet recovery were estimated according to the Kaplan-Meier method and were evaluated with the log-rank test. The JMP program (SAS Institute Inc) was used for these analyses. All analyses were performed according to the intention-to-treat principle. All statistical tests except the method of Blackwelder were 2-sided, and the significance level was set at .05.
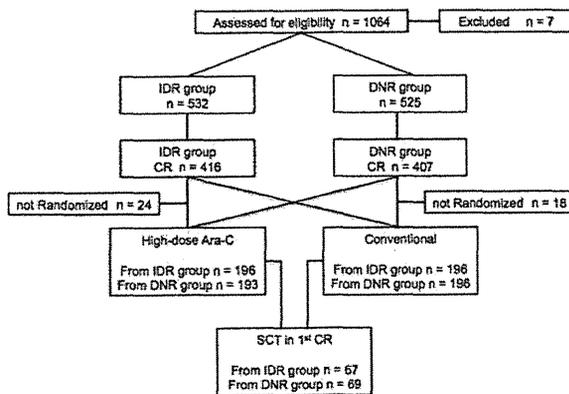
Figure 1. CONSORT flow diagram. IDR indicates idarubicin; DNR, daunorubicin; CR, complete remission; Ara-C, cytarabine; and SCT, stem cell transplantation.

Results

Patient characteristics

Among 1064 registered patients, 7 did not meet the inclusion criteria (misdiagnosis, 1; infectious complication, 1; without therapy, 1; and withdrawal of consent, 4). The study population thus comprised 1057 patients (Figure 1). Patient characteristics are presented in Table 1. Median age was 47 years (range, 15-64 years). Cytogenetics data were available for 1021 patients (96.6%). Among these, 247 (24.2%) were classified in the favorable-risk group, 681 (66.7%) in the intermediate-

Table 1. Patient characteristics

	IDR group (n = 532)	DNR group (n = 525)	P
Median age, y (range)	47 (15-64)	47 (15-64)	.781
≤ 50	310	306	
> 50	222	219	.996
Median WBC count, ×10⁹/L (range)	13.7 (0.1-382)	15.3 (0.1-334)	.769
≤ 20 × 10⁹/L	304	297	
20= ≤ 50 × 10⁹/L	95	104	
> 50 × 10⁹/L	125	121	
Unknown	8	3	.427
FAB type			
M0	30	30	
M1	95	94	
M2	232	233	
M4	100	100	
M5	56	51	
M6	17	16	
M7	2	1	.997
Cytogenetic group			
Favorable	128	119	
Intermediate	335	346	
Adverse	49	44	
Unknown	20	16	.561
MPO-positive blasts, %			
< 50	169	187	
≥ 50	307	292	
Unknown	56	46	.330
Performance status			
0, 1, 2	512	509	
3	20	16	.524

Values are number of patients unless otherwise indicated.

IDR indicates idarubicin; DNR, daunorubicin; WBC, white blood cell count; FAB, French-American-British classification; and MPO, myeloperoxidase.

Table 2. Results of induction therapy

	IDR group, n (%)	DNR group, n (%)
Patients	532	525
CR	416 (78.2)	407 (77.5)
CR by 1 course	341 (64.1)	321 (61.1)
CR by 2 courses	75 (14.1)	86 (16.4)
95% CI	74.5-81.5	73.8-80.9

IDR indicates idarubicin; DNR, daunorubicin; and CR, complete remission.

risk group, and 93 (9.1%) in the adverse group. Five hundred thirty-two patients were assigned to the idarubicin group and 525 to the daunorubicin group. The 2 groups were well balanced with regard to pretreatment characteristics such as age, initial WBC counts, FAB classification, and cytogenetic prognostic grouping.

Response to induction therapy

Overall, of 1057 evaluable patients, 823 (77.9%) achieved CR. Of 532 patients in the idarubicin group, 416 (78.2%) achieved CR, and of 525 in the daunorubicin group, 407 (77.5%) obtained CR ($P = .79$). Noninferiority for the primary end point was assessed by determining whether the lower bound of the 95% confidence interval (CI) of the difference between the CR rates for the daunorubicin and idarubicin groups was less than −10%. The CR rate of the daunorubicin group was noninferior to that of the idarubicin group (Table 2). In the idarubicin group, 341 patients (64.1%) achieved CR after the first course, and in the daunorubicin group, 321 (61.1%) did so ($P = .39$). The average period to achieve CR was 33.8 days (95% CI 32.9 to 34.6 days) in the idarubicin group and 32.4 days (95% CI 31.6 to 33.2 days) in the daunorubicin group ($P = .038$). CR rates related to FAB classification, age, and cytogenetics are shown in Table 3. Although they were few, patients with FAB M6 responded better to idarubicin: 78% of 17 patients in the idarubicin group and 38% of 16 in the daunorubicin group achieved CR ($P = .037$). There were no differences in CR rate between the 2 groups in other FAB subtypes, cytogenetic risk groups, age, myeloperoxidase positivity of blasts, initial WBC count, or performance status (Table 3). Overall, logistic regression analysis revealed that induction regimen was not an independent prognostic factor but that cytogenetic group and percentage of myeloperoxidase-positive blasts were significant independent factors for achieving CR (Table 4). A cutoff value of WBCs at 20 or 50 × 10⁹/L did not change the result.

OS and RFS

At a median follow-up of 48 months, 5-year predicted OS rates were 48% for the idarubicin group (95% CI 43% to 53%) and 48% for the daunorubicin group (95% CI 43% to 53%; $P = .54$; Figure 2A), and 5-year predicted RFS rates of CR patients were 41% (95% CI 36% to 46%) and 41% (95% CI 35% to 45%), respectively ($P = .97$; Figure 2B). Significant unfavorable prognostic features for OS by the Cox proportional hazard model were adverse cytogenetic risk group, age greater than 50 years, WBC count more than 20 × 10⁹/L, myeloperoxidase-positive blasts less than 50%, and FAB classification of either M0, M6, or M7; for RFS, the significant unfavorable prognostic features were adverse cytogenetic risk group, WBC count more than 20 × 10⁹/L, myeloperoxidase-positive blasts less than 50%, lactate dehydrogenase of 500 IU/L or more, and age greater than 50 years. Induction regimen was not an independent prognostic factor for either OS or RFS by this multivariate analysis.

Table 3. CR rates by induction therapy

	CR rate, %		
	IDR group (n = 532)	DNR group (n = 525)	P
FAB type			
M0	43	63	.195
M1	86	79	.236
M2	80	82	.718
M4	81	79	.86
M5	77	75	.96
M6	76	38	.037
M7	50	100	.999
Cytogenetic group			
Favorable	91	96	.134
Intermediate	79	76	.359
Adverse	51	43	.534
Unknown	50	69	.257
Age, y			
≤ 50	83	77	.108
> 50	73	78	.225
Myeloperoxidase-positive blasts, %			
< 50	68	66	.709
≥ 50	87	88	.699
WBC at diagnosis, ×10⁹/L			
≤ 20	79	76	.767
20= ≤ 50	82	82	.993
> 50	74	77	.824
Performance status			
0, 1, 2	79	78	.762
3	80	75	.999

CR indicates complete remission; IDR, idarubicin; DNR, daunorubicin; FAB, French-American-British classification; and WBC, white blood cell count.

Adverse events

Patients receiving idarubicin required a slightly but significantly longer time to recover from neutropenia and thrombocytopenia. Median duration with a neutrophil count less than 1.0×10^9/L was 28 days for the idarubicin group and 27 days for the daunorubicin group ($P = .0011$; Figure 3A). Median duration with a platelet count less than 100×10^9/L was 25 days for the idarubicin group and 24 days for the daunorubicin group ($P = .0034$; Figure 3B). Sepsis occurred more frequently in the idarubicin group than in the daunorubicin group (8.7% and 4.9%, respectively; $P = .02$). Early death within 60 days occurred more frequently in the idarubicin group than in the daunorubicin group (4.7% and 2.1%, respectively; $P = .03$; Table 5).

Postremission therapy

Of the 823 CR patients, 781 were randomly assigned to receive either 4 courses of conventional standard-dose consolidation

Table 4. Factors that predicted CR in all evaluable patients by multivariate analysis

Variables	Odds ratio	P
Cytogenetic group		
Favorable	10.39	< .0001
Intermediate	4.67	< .0001
Myeloperoxidase-positive blast ≥ 50%	2.64	< .0001
Induction therapy: IDR arm	0.97	.854

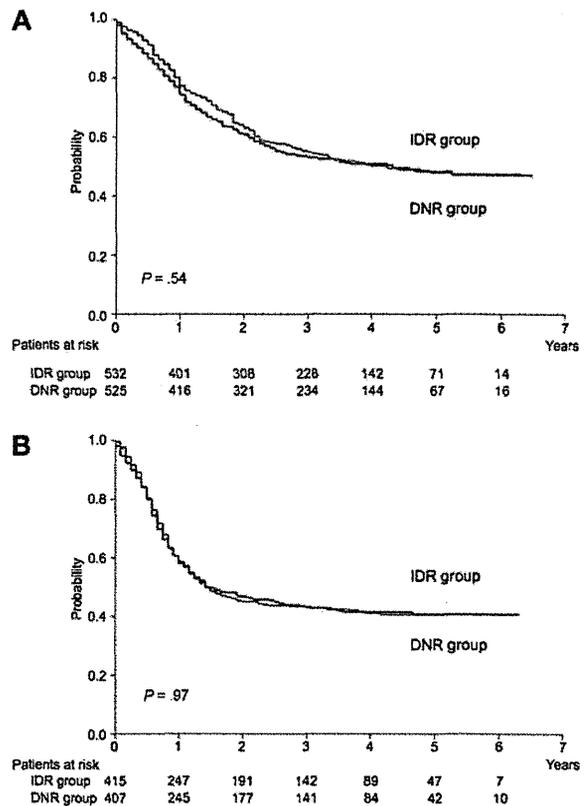CR indicates complete remission; and IDR, idarubicin.

Figure 2. OS and RFS. (A) Predicted 5-year overall survival (OS) was 48% for the idarubicin group (IDR; n = 532; red line) and 48% for the daunorubicin group (DNR; n = 525; blue line; P = .54). (B) Predicted 5-year relapse-free survival (RFS) was 41% for the idarubicin group (IDR; n = 416; red line) and 41% for the daunorubicin group (DNR; n = 407; blue line; P = .97).

therapy (392 patients) or 3 courses of high-dose Ara-C therapy (389 patients), and 136 patients (16% of CR patients) underwent allogeneic SCT in the first CR. There was no significant difference in OS or RFS by postremission therapy between the idarubicin and daunorubicin groups (Table 6). In the idarubicin group, predicted 5-year OS rates were 57% for the conventional standard-dose consolidation arm (95% CI 49% to 65%) and 58% for the high-dose Ara-C arm (95% CI 51% to 66%; $P = .79$; Figure 4A). In the daunorubicin group, predicted 5-year OS rates were 56% (95% CI 48% to 63%) and 58% (95% CI 50% to 65%; $P = .71$; Figure 4B), respectively. If 2 groups were evaluated together, predicted 5-year OS rates were 56% (95% CI 51% to 62%) and 58% (95% CI 53% to 62%; $P = .95$), and predicted 5-year RFS rates were 39% (95% CI 34% to 44%) and 43% (95% CI 38% to 48%), respectively ($P = .72$). The detailed results of this consolidation phase will be reported in a separate paper.[22]

Discussion

The present randomized study demonstrates that if the dose intensity is increased appropriately, daunorubicin is as effective as a standard dose of idarubicin for adults less than 65 years of age
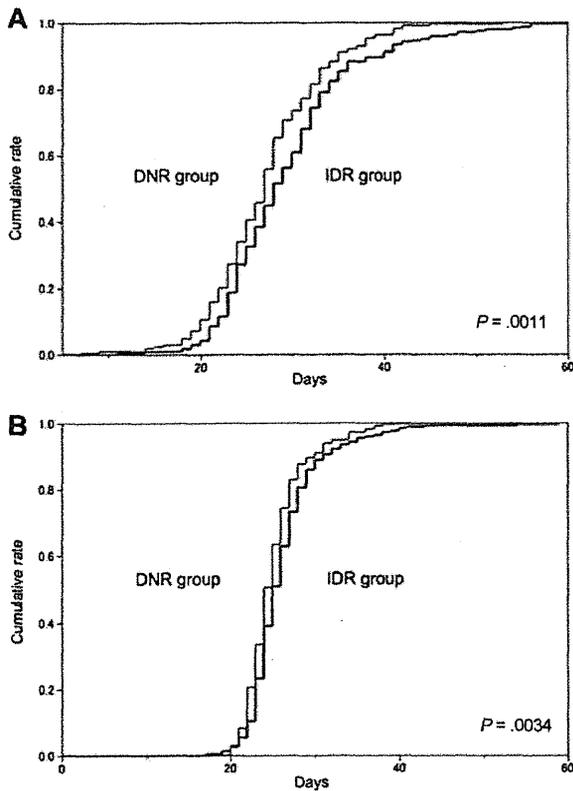
A

B

Figure 3. Hematologic recovery. (A) Day of recovery from neutropenia after the first induction course. Neutropenia was defined as neutrophil count < 1.0 × 10⁹/L. Median duration until recovery was 28 days for the idarubicin group (IDR; red line) and 27 days for the daunorubicin group (DNR; blue line; P = .0011). (B) Day of recovery from thrombocytopenia after the first induction course. Thrombocytopenia was defined as platelet count < 100 × 10⁹/L. Median duration until recovery was 25 days for the idarubicin group (IDR; red line) and 24 days for the daunorubicin group (DNR; blue line; P = .0034).

who have been newly diagnosed with AML. Remission-induction therapy with 50 mg/m² of daunorubicin for 5 days resulted in almost the same CR rate and long-term outcome as seen with 12 mg/m² of idarubicin for 3 days in combination with 100 mg/m² of Ara-C for 7 days. Generally, daunorubicin is used at a dose of 45 to 50 mg/m² for 3 days in combination with 100 to 200 mg/m² of Ara-C for 7 days, and 50% to 70% of newly diagnosed adult patients with AML achieve CR. As stated in the "Introduction," JALSG used a response-oriented individualized induction therapy in the AML87, AML89, and AML92 studies for AML, which permitted the additional daunorubicin and other antileukemia drugs

Table 5. Adverse events (World Health Organization grades 3 to 5) after the start of induction therapy

	IDR group, no. of patients (%)	DNR group, no. of patients (%)	P
Sepsis	46 (8.7)	26 (4.9)	.021
Early death*	25 (4.7)	11 (2.1)	.026
Bleeding	19 (3.6)	23 (4.4)	.532
Febrile neutropenia	416 (78.2)	406 (77.4)	.761
Acute cardiac toxicity	10 (1.9)	4 (0.8)	.112
Late-onset cardiac failure	2 (0.38)	2 (0.38)	.998

IDR indicates idarubicin; and DNR, daunorubicin.
*Death within 60 days after the start of induction therapy.

Table 6. Effect of induction therapy on outcome by postremission therapies

	5-year OS		5-year RFS	
Consolidation arm	IDR group	DNR group	IDR group	DNR group
Conventional standard-dose, %	57	56	41	37
P		.759		.332
High-dose Ara-C, %	58	58	42	44
P		.725		.658
Allogeneic SCT in first CR, %	59	59	58	64
P		.469		.394

Number of patients in the conventional standard-dose arm was 196 in the IDR group and 196 in the DNR group; in the high-dose Ara-C arm, the numbers were 196 and 193, respectively; and in the SCT group, the numbers were 67 and 69, respectively, as shown in Figure 1.

OS indicates overall survival; RFS, relapse-free survival; IDR, idarubicin; DNR, daunorubicin; Ara-C, cytarabine; and CR, complete remission.

to be administered according to bone marrow status on day 8 or later.[12-14] The CR rates in these 3 studies ranged from 77% to 80%, and the median total dose of daunorubicin was 240 mg/m².

On the basis of these experiences and also because of the regulation of our national medical insurance system, we used a dose and schedule of daunorubicin of 50 mg/m² for 5 days, that is, a total dose of 250 mg/m². In addition,we avoided higher daily doses, such as 80 mg/m² for 3 days, because higher plasma concentration might cause more cardiotoxicity in older patients.[23]
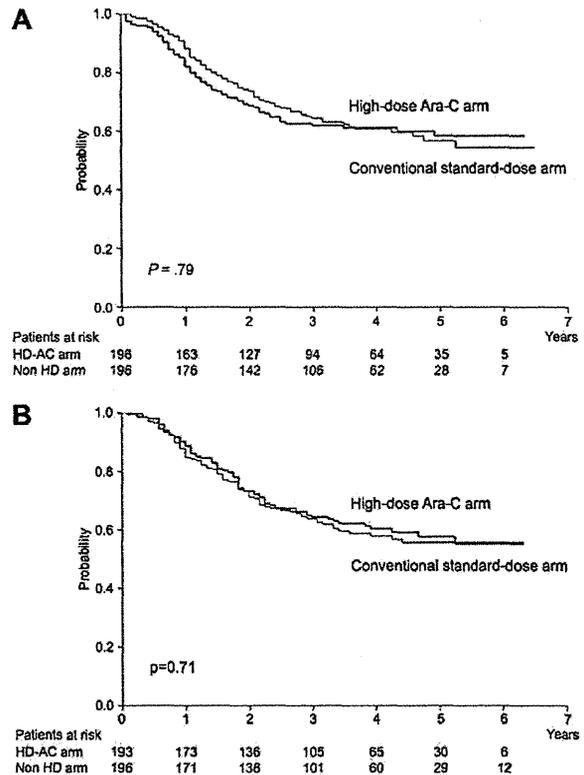
A

B

Figure 4. OS of CR patients randomized to receive consolidation therapy. (A) In the idarubicin group, predicted 5-year OS was 58% for the high-dose Ara-C arm (n = 196; red line) and 57% for the conventional standard-dose arm (n = 196; blue line; P = .759). (B) In the daunorubicin group, predicted 5-year OS was 58% for the high-dose Ara-C arm (n = 193; red line) and 56% for the conventional standard-dose arm (n = 196; blue line; P = .71). Ara-C indicates cytarabine; HD-AC arm, high-dose Ara-C arm; and Non HD arm, conventional standard-dose arm.

Three randomized studies in the early 1990s[4-6] and subsequent studies[24,25] and meta-analyses[7] reported a superior effect of idarubicin (12 to 13 mg/m² × 3 days) over that of daunorubicin (45 to 50 mg/m² × 3 days), in combination with Ara-C, and AML patients receiving idarubicin obtained 70% to 80% CR without a significant increase in toxic mortality, whereas those receiving daunorubicin achieved 58% to 65% CR.[4-6] However, because the duration of neutropenia and thrombocytopenia was longer in the idarubicin groups, it was questioned whether the doses used in these comparisons were equivalent in terms of levels of toxicity and whether any observed advantage represented an inherent biological advantage of idarubicin rather than biological dose equivalence.[1,2]

In these randomized studies, Wiernik et al reported that patients with initial WBC counts > 50 × 10⁹ cells/L obtained only 32% CR by the daunorubicin regimen compared with 68% CR by the idarubicin regimen, whereas patients with WBC counts < 50 × 10⁹/L obtained 65% and 69% CR, respectively.[5] Berman et al also reported that patients in the idarubicin group did well regardless of their initial WBC count, whereas patients in the daunorubicin group had a decreased response rate as the WBC count increased.[4] In the present study, however, a total of 250 mg/m² of daunorubicin resulted in almost the same CR rate as a total dosage of 36 mg/m² of idarubicin regardless of initial WBC counts and other prognostic factors such as cytogenetics, age, and FAB classification except M6. Although among patients with FAB M6, 16 patients in the daunorubicin group had a significantly lower CR rate than 17 patients in the idarubicin group, we have no clear explanation for this observation, because the small number of patients made further analysis difficult. Thus, the increased total dosage of daunorubicin administered in 5 days would be responsible for almost the same satisfactory CR rate and long-term outcome as idarubicin administered in 3 days in the present study. As for adverse events, the recovery from neutropenia and thrombocytopenia was slightly but significantly delayed in the idarubicin group, and sepsis and early mortality occurred more frequently in the idarubicin group, as shown in Figure 3 and Table 5.

Before we initiated the present AML201 study, there was no evidence that a higher dose of daunorubicin was more effective than its standard dose because of the lack of a prospective randomized study. In the sequential studies reported by Southwest Oncology Group, however, the CR rate with daunorubicin at a dose of 70 mg/m² was better than that with 45 mg/m².[26,27] Very recently, 2 groups reported that a higher dose of daunorubicin improved the CR rate and OS in prospective randomized studies.[28,29] A collaborative group composed of the Dutch-Belgian Cooperative Trial Group for Hemato-Oncology, the German AML Study Group, and the Swiss Group for Clinical Cancer Research compared 3-day daunorubicin at 90 mg/m² with 3-day daunorubicin at 45 mg/m², in combination with 7-day Ara-C, in elderly patients 60 to 83 years of age who had AML or high-risk refractory anemia and reported a higher CR rate for the escalated-treatment group (52% vs 35%, P = .002).[28] Although survival end points did not differ significantly overall, among patients 60 to 65 years of age, the CR rate (73% vs 51%) and OS rate (38% vs 23%) were significantly higher for the 90-mg/m² group. The Eastern Cooperative Oncology Group also compared 3-day daunorubicin at 90 mg/m² with 3-day daunorubicin at 45 mg/m², in combination with 7-day Ara-C, in patients 17 to 60 years of age with AML and reported a higher CR rate (70.6% vs 57.3%, P < .001) and longer OS (median 23.7 vs 15.7 months, P = .003) for the high-dose group.[29] Given these

previous reports and the present report, the optimal total dose of daunorubicin is still to be explored but may rest somewhere between 250 and 270 mg/m². Because we used the FAB classification in the present study, we did not include either patients with 20% to 30% of blasts in the bone marrow or those with refractory anemia with excess blasts; therefore, it is unclear whether the present result is applicable to those patients.

Idarubicin is a derivative of daunorubicin and differs from its parent compound by the deletion of a methoxy group at position 4 of the chromophore ring. In vitro and preclinical data have shown that idarubicin is more lipophilic, is faster in cellular uptake, exhibits increased cellular retention, is lower in susceptibility to P-glycoprotein–dependent resistance, and is less cardiotoxic than daunorubicin. Both idarubicin and daunorubicin undergo conversion to their respective alcohol metabolites, idarubicinol and daunorubicinol. Unlike the latter, idarubicinol has a prolonged plasma half-life and is thought to have a pharmacologic advantage.[30-33]

The pediatric Berlin-Frankfurt-Münster group previously compared idarubicin 12 mg/m² for 3 days with daunorubicin 30 mg/m² twice daily for 3 days, in combination with Ara-C and etoposide, and reported almost the same CR rates (85% vs 86%, respectively) and predicted 5-year event-free survival (55% vs 49%, respectively, P = .29) in newly diagnosed childhood AML.[34] Furthermore, daunorubicin at a dose of 60 mg/m² for 3 days and idarubicin at a dose of 12 mg/m² for 3 days achieved similar CR rates in the studies by Eastern Cooperative Oncology Group that consisted of a large number of adult patients.[35,36]

Recently, the French Acute Leukemia Association reported a randomized study comparing standard doses of idarubicin (12 mg/m² for 3 days) with high doses of daunorubicin (80 mg/m² for 3 days) or idarubicin (12 mg/m² for 4 days) for remission induction in newly diagnosed elderly patients 50 to 70 years of age (median 60 years old) with AML.[37] CR rates were significantly higher for the standard-dose idarubicin group (83%) than for the high-dose daunorubicin group (70%, P = .007) but not for the high-dose idarubicin group (78%, P = .12). Although OS, relapse incidence, and event-free survival were not different among the 3 arms of the study, daunorubicin (80 mg/m² for 3 days) did not improve the CR rate of elderly AML patients to the level of the standard-dose idarubicin regimen.

With regard to adverse events, recovery from myelosuppression was faster and sepsis was less frequent in the daunorubicin group. Both acute and late-onset cardiotoxicity were reported only in a small number of patients in both groups. Given that there was no increase in severe cardiac toxicities in patients receiving high-dose daunorubicin (90 mg/m² for 3 days) compared with standard-dose daunorubicin (45 mg/m² for 3 days) in the Eastern Cooperative Oncology Group study (7.9% and 7.2%, respectively),[29] daunorubicin may not necessarily be administered for 5 days as in the present study (50 mg/m² for 5 days), although further follow-up observation is needed for late-onset cardiotoxicity.

Since the landmark study of the Cancer and Leukemia Group B,[38] it has been believed that high-dose Ara-C is superior to consolidation therapy with intermediate (400 mg/m² for 5 days) or conventional (100 mg/m² for 5 days) doses of Ara-C. In the present study, we prospectively compared high-dose Ara-C with consolidation therapy that included a conventional dose of Ara-C and non–cross-resistant agents. Our results clearly demonstrate that there is no difference in RFS and OS between the 2 consolidation arms, regardless of whether idarubicin or daunorubicin is used as induction chemotherapy.