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# V. 研究成果の刊行物・別刷

Cancer Science
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# Phase I trial of gemtuzumab ozogamicin in intensive combination chemotherapy for relapsed or refractory adult acute myeloid leukemia (AML): Japan Adult Leukemia Study Group (JALSG)-AML206 study

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**In order to investigate better molecular-target therapy for acute myeloid leukemia (AML), we conducted a phase I trial of a combination of gemtuzumab ozogamicin (GO) with conventional chemotherapy. Between January 2007 and December 2009, a total of 19 adult Japanese patients with relapsed or refractory CD33-positive AML (excluding acute promyelocytic leukemia) were enrolled. All registered patients received a standard dose of cytarabine (Ara-C) (100 mg/m$^2$ × 7 days), combined with either idarubicin (IDR) (10–12 mg/m$^2$ × 3 days) or daunorubicin (DNR) (50 mg/m$^2$ × 3–5 days), and then GO (3–5 mg/m$^2$), which was administered 1 day after the last infusion of IDR (IAG regimen) or DNR (DAG regimen). While doses of both GO and IDR and the administration period of only DNR were increased, the dose-limiting toxicity (DLT) was assessed. Among 19 patients (nine in the IAG regimen, 10 in the DAG regimen), the median age was 59 years (range 33–64), and the relapsed/refractory ratio was 13/6. In the therapy using 3 mg/m$^2$ GO in the IAG or DAG regimen, grade 3/4 leukopenia and neutropenia were observed in all patients, but none had grade 3/4 non-hematological toxicities, except febrile neutropenia. Three patients in the IAG regimen who were administered 5 mg/m$^2$ GO showed DLT. No patients had veno-occlusive disease or sinusoidal obstructive syndrome. In conclusion, 3 mg/m$^2$ GO combined with Ara-C and IDR or DNR can be safely administered, and phase II trials should be conducted to investigate the clinical efficacy of the combination therapy. (*Cancer Sci* 2011; 102: 1358–1365)**

Current standard induction treatment for acute myeloid leukemia (AML) involves drug regimens with two or more agents that include an anthracycline or anthraquinone and cytarabine (Ara-C).[1–6] A recent clinical trial of the Japan Adult Leukemia Study Group (JALSG) for younger adult patients (16–64 years of age) with newly diagnosed AML showed a 77.9% complete remission (CR) rate.[4] Remission rates achieved by us and others range approximately 55–90% in adult patients, depending on the composition of the population treated.[1–6] However, these high CR rates did not always translate into improved outcomes for patients, mainly because approximately 40–50% eventually relapsed. Although there are various clinical trials for patients with relapsed or refractory AML, the probability of a second CR is approximately 50% in younger patients, but the duration of CR is nearly always much shorter than the first CR. No standard chemotherapy regimen provides a high rate and durable CR for patients with relapsed/refractory AML, and all such patients should be considered eligible for clinical trials if available.[7]

Among newer antileukemia agents being examined for the treatment of AML, an antibody to CD33 antigen is one of the most promising drugs. The CD33 antigen is expressed on 80–90% of AML blasts and acts as a target for antibody-mediated destruction. Gemtuzumab ozogamicin (GO) is a recombinant humanized anti-CD33 monoclonal antibody conjugated to calicheamicin (a cytotoxin), which is 1000 times as potent as doxorubicin.[8,9] This conjugated antibody is rapidly internalized and causes subsequent apoptosis.[10] GO was shown to be effective in patients with relapsed AML in nonrandomized studies and gained regulatory approval in the United States (the US Food and Drug Administration [FDA]) for relapsed older patients (older than 60) with AML.[11,12] GO was also approved by the Japanese government in 2005 for use in patients with relapsed/refractory AML, but only for monotherapy based on a phase I/II study for Japanese patients.[13] GO does not cause alopecia or mucositis, even though it causes myelosuppression, an infusional syndrome, and liver damage such as hyperbilirubinemia and/or hepatic transaminitis (or elevation of transaminase). Several studies have indicated that GO combined with conventional chemotherapy would provide a more potent antileukemia effect than GO monotherapy.[14–19] We considered that addition of GO to conventional chemotherapy in induction therapy would improve the clinical outcome of AML patients of all ages. To find the optimal usage of GO in combination with conventional chemotherapy for relapsed or refractory AML, we conducted a phase I study. Here we report the results of this JALSG-AML206 trial in adult patients with relapsed or refractory AML, younger than age 65, in which the dosage of GO, combined with our two types of standard remission induction therapy for de novo AML, were tested.[4]

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## Materials and Methods

**Patient eligibility.** Between January 2007 and December 2009, 19 eligible patients with relapsed and refractory AML were enrolled in the present study. The inclusion criteria were as follows: (i) diagnosed as $CD33^+$AML (excluding acute promyelocytic leukemia); (ii) relapsed ≥6 months after the first CR (CR1) or were refractory to initial standard induction therapy; (iii) age: 20–64 years old; (iv) 0–2 by the Eastern Cooperative Oncology Group (ECOG) performance status; (v) no active double cancer; (vi) adequate cardiac, renal and hepatic function with left ventricular ejection fraction ≥50%, creatinine ≤2.0 mg/dL, bilirubin ≤1.5 mg/dL; (vii) no uncontrolled infection; and (viii) no human immunodeficiency virus (HIV) infection. Patients who received more than 500 mg/m$^2$ of daunorubicin (DNR) in a prior therapy were ineligible to DNR-including protocol. Cytogenetic abnormalities were grouped by standard criteria and classified according to the UK Medical Research Council (MRC) classification.[20]

**Study design.** The study was conducted by six designated institutions among JALSG members, and consisted of two parts: idarubicin (IDR), Ara-C plus GO (IAG regimen), and DNR, Ara-C plus GO (DAG regimen). The treatment schedules of both regimens are shown in Figure 1.

*IAG regimen.* The starting doses (level 1) consisted of IDR 10 mg/m$^2$ administered intravenously (d.i.v.) over 30 min daily for three consecutive days (days 1–3), Ara-C 100 mg/m$^2$ as a continuous intravenous infusion (c.i.v.) for seven consecutive days (days 1–7) and GO 3 mg/m$^2$ for 2 h d.i.v. on day 4. While the dose and schedule of Ara-C were fixed, doses of IDR and GO were increased in levels 2 and 3 as shown in Figure 1.

*DAG regimen.* The starting doses (level 1) consisted of DNR 50 mg/m$^2$ administered d.i.v. over 30 min daily for three consecutive days (days 1–3), Ara-C 100 mg/m$^2$ c.i.v. (days 1–7) and GO 3 mg/m$^2$ for 2 h d.i.v. on day 4. While the dose and schedule of Ara-C were fixed, doses of DNR and GO were scheduled to increase in levels 2, 3 and 4 (Fig. 1).

All patients were hospitalized during therapy and received optimal supportive care. For prophylaxis of GO infusion reaction, antihistamines and corticosteroids were given 1 h before the infusion. Granulocytopenic patients were placed in single rooms with conventional isolation or in laminar airflow rooms. Broad-spectrum antibiotics were given for fever higher than 38°C in the presence of granulocytopenia, and were continued until defervescence and recovery of granulocyte counts above $0.5 \times 10^9$/L. Random donor platelet concentrates were administered to maintain a platelet count above $20 \times 10^9$/L. Packed red blood cell (RBC) transfusions were performed to maintain hemoglobin above 7.0 g/dL.

**Response criteria.** Responses were evaluated according to the recommendations of the International Working Group.[21] A CR was defined as disappearance of all clinical and/or radiological evidence of disease with ≤5% marrow blasts, neutrophil (ANC) count $\geq 1 \times 10^9$/L and platelet (PLT) count $\geq 100 \times 10^9$/L. A CR without PLT recovery (CRp) had identical marrow results and ANC recovery as for CR, but with PLT $<100 \times 10^9$/L and $\geq 20 \times 10^9$/L. Partial remission consisted of a peripheral blood recovery as for CR, but with a decrease in marrow blasts of ≥50% compared with baseline before therapy, and not more than 6–25% blasts in the marrow. All other responses were considered failures. After the IAG or DAG treatment, patients received the most appropriate AML therapy determined by their individual physicians.

**Adverse events/toxicities.** During the entire period of induction, blood cell counts were performed daily and liver and renal

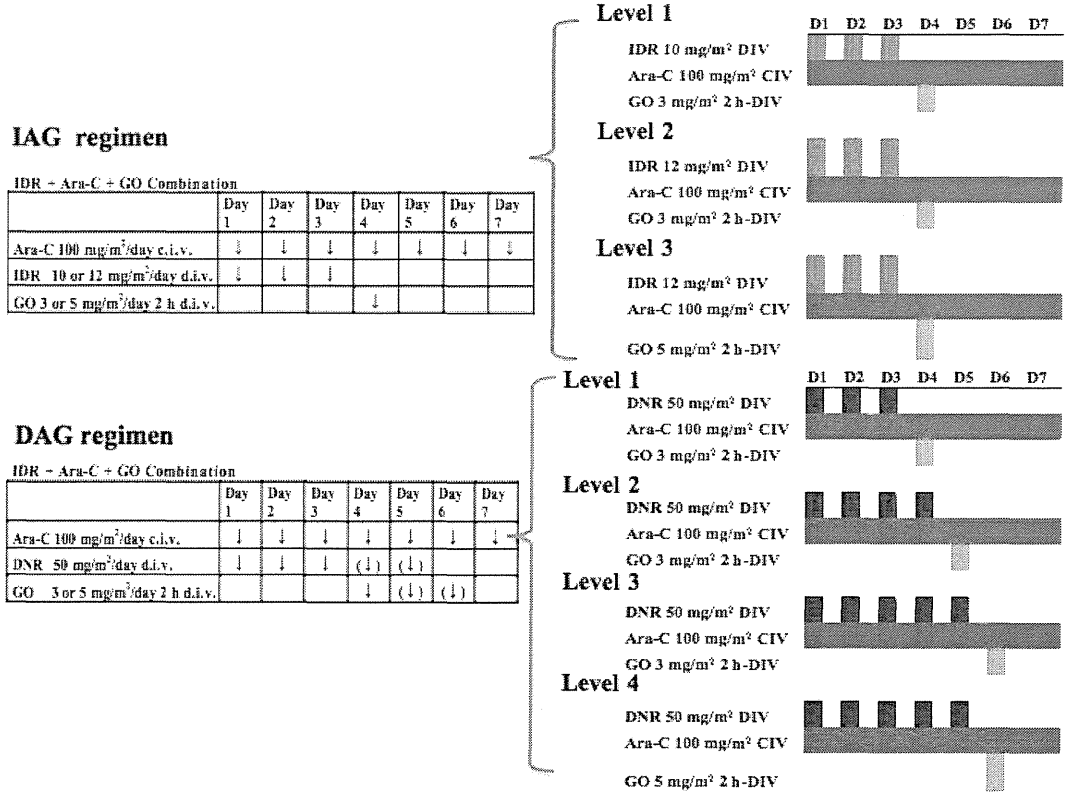


**Fig. 1.** Treatment schedule of the Japan Adult Leukemia Study Group (JALSG)-AML206 study. Ara-C, cytarabine; CIV and c.i.v., continuous intravenous infusion; DIV and d.i.v., drip intravenous infusion; DNR, daunorubicin; GO, gemtuzumab ozogamicin; IDR, idarubicin.

**Table 1. Patient characteristics**

| | Overall ($n$ = 19) | IAG regimen ($n$ = 9) | DAG regimen ($n$ = 10) |
|---|---|---|---|
| Male:Female | 9:10 | 4:5 | 5:5 |
| Age (years)† | 59 (33–64) | 61 (52–64) | 58 (33–62) |
| ≤60 | 10 | 3 | 7 |
| >60 | 9 | 6 | 3 |
| WBC ($\times 10^9$/L)† | 3.0 (1.0–39.2) | 3.7 (2.6–39.2) | 2.05 (1.0–25.3) |
| Blast (%)† | 42.8 (7.9–96.8) | 56.4 (17.3–88.0) | 29.9 (7.9–96.8) |
| CD33 positivity in blast (%)† | 89.4 (39.0–100) | 92.9 (62.8–100) | 80.6 (39.0–96.9) |
| Disease status | | | |
| Relapsed/Refractory | 13/6 | 7/2 | 6/4 |
| FAB type (no. patients) | | | |
| M0 | 1 | | 1 |
| M1 | 3 | 2 | 1 |
| M2 | 8 | 3 | 5 |
| M4 | 6 | 3 | 3 |
| M5 | 1 | 1 | |
| Cytogenetic group (no. patients) | | | |
| Favorable | 2 | 1 | 1 |
| Intermediate | 11 | 6 | 5 |
| Adverse | 6 | 2 | 4 |
| Performance status (no. patients) | | | |
| 0 | 1 | 0 | 1 |
| 1 | 18 | 9 | 9 |

†Median value and range in parentheses. FAB, French-American-British Classification; WBC, white blood cells.

blood tests three times weekly. Electrocardiography (ECG) was also performed once a week.

Hematological and non-hematological toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) ver 3.0, National Institutes of Health.

**Statistical analysis.** The primary objective of the study was to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of GO in combination with standard chemotherapy in Japanese patients. Dose escalation of anthracycline and GO in the IAG or DAG treatment followed a standard 3 + 3 phase I design in which cohorts of three patients at a time were treated at a dose and schedule level. If no DLT was observed, the next cohort was escalated to the next level. If one or two of the first three patients experienced a DLT, up to a total of six patients were enrolled at the same dose level. The next cohort was escalated only if a total of less than two patients presented with a DLT. If three of the first three patients experienced a DLT, the dose-escalation was stopped and the prior dose level was considered the MTD.

All ≥grade 3 drug-related nonhematological toxicities that occurred after treatment were considered DLT, with the exception of nausea and vomiting (if manageable with supportive care), alopecia, drug-related fevers, asymptomatic abnormalities of lactate dehydrogenase, alkaline phosphatase, disturbances of electrolytes and febrile neutropenia (FN) as these are common events in patients with relapsed AML.

Myelosuppression was not considered a DLT except for prolonged bone marrow aplasia longer than 6 weeks (or 42 days). Secondary objectives were to evaluate the efficacy of these treatment regimens.

The study was approved by the Institutional Review Board 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 the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (http://www.umin.ac.jp/ctr/) as UMIN000001141 and UMIN000001142.

## Results

**Patient characteristics.** A total of 19 patients with relapsed or refractory $CD33^+$AML were enrolled and evaluated (Table 1). The median age of patients was 59 years (range 33–64), the male/female ratio was 9/10, and the relapsed/refractory ratio was 13/6. The median value of blasts in the bone marrow before treatment was 42.8% (range 7.9–96.8%), and the median expression of CD33 antigen was 89.4% (range 39–100%). Patient characteristics in the IAG and DAG groups were similar, with the exception of age. Patients older than 60 years were more frequently enrolled in the IAG regimen. Among adverse cytogenetic groups, four patients had complex karyotypes (two in each group), one had t(6:9) in the DAG group and one had inv(5)del(7) in the DAG group.

**Safety.** *In the IAG regimen.* Hematological toxicities were commonly observed as expected for re-induction therapy (Table 2). Levels of white blood cells (WBC) at the time of GO administration tended to be lower than $3.0 \times 10^9$/L and those of ANC were $<1.5 \times 10^9$/L. Grade 4 leukopenia and neutropenia

**Table 2. IAG regimen: hematological toxicities**

| | Level 1 ($n$ = 3) (IPt-1/IPt-2/IPt-3) | Level 2 ($n$ = 3) (IPt-4/IPt-5/IPt-6) | Level 3 ($n$ = 3) (IPt-7/IPt-8/IPt-9) |
|---|---|---|---|
| WBC ($\times 10^9$/L) at GO administration | 2.4/1.1/5.4 | 1.3/0.4/2.3 | 0.8/1.2/3.0 |
| WBC (grade 3/4) | 0/3 | 0/3 | 0/3 |
| Days to nadir after GO administration | 4/6/13 | 10/5/10 | 6/5/7 |
| ANC ($\times 10^9$/L) at GO administration | 1.7/1.5/4.4 | 0.5/0/1.0 | 0.3/0.2/0.4 |
| ANC (grade 3/4) | 0/3 | 0/3 | 0/3 |
| Days to nadir after GO administration | 11/6/10 | 7/5/7 | 6/13/7 |
| Days toward ANC recovery | 31/35/26 | 24/34/35 | 42/38/24 |
| PLT ($\times 10^9$/L) at GO administration | 62/64/146 | 24/51/159 | 87/23/44 |
| PLT (grade 3/4) | 3/0 | 2/1 | 2/1 |
| Days to nadir after GO administration | 8/8/14 | 10/10/14 | 11/5/14 |
| PLT transfusion (units) | 90/130/100 | 130/130/50 | 70/220/70 |
| Days toward PLT recovery | 31/NA/NA | NA/43/35 | 25/87/31 |
| Hemoglobin (grade 0/1/2/3/4) | 0/1/2/0/0 | 0/1/2/0/0 | 1/1/1/0/0 |
| RBC transfusion (units) | 4/4/12 | 4/6/2 | 8/16/4 |

ANC, neutrophils; GO, gemtuzumab ozogamicin; NA, data was not available because the next treatment proceeded before platelet recovery due to disease progression; PLT, platelets; RBC, red blood cells; WBC, white blood cells.



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**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/m$^2$ 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/m$^2$ 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 ($\times 10^9$/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 ($\times 10^9$/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 ($\times 10^9$/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/



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**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/m$^2$ i.v. q12 h/day, days 2–4<br>Aa-C: 500 mg/m$^2$ 2 h d.i.v. q12 h/day, days 2–4<br>CSA: 6 mg/kg 2 h d.i.v. + 16 mg/kg c.i.v., days 1, 2 | 4.5 mg/m$^2$ 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/m$^2$/day i.v., days 2–4<br>Ara-C: 1.5 g/m$^2$/day, days 2–5 | 6 mg/m$^2$ 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/m$^2$ 2 h d.i.v. q12 h/day, days 1–5<br>MIT: 12 mg/m$^2$/day i.v., days 1–3 | 9 mg/m$^2$ 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<br>Ara-C: 100 mg/m$^2$/day c.i.v., days 2–8 or 4–8 | 6 mg/m$^2$ 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/m$^2$ 3 h d.i.v./day, days 1–5 | 9 mg/m$^2$ 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.

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## Disclosure Statement

The authors have no conflict of interest.

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## Impact of additional chromosomal abnormalities in patients with acute promyelocytic leukemia: 10-year results of the Japan Adult Leukemia Study Group APL97 study

The t(15;17) chromosome translocation in acute promyelocytic leukemia is classified as a favorable cytogenetic feature among acute myeloid leukemia patients.[1-4] However, the prognostic impact of additional chromosomal abnormalities (ACAs) in acute promyelocytic leukemia has been debated.[5-9] We analyzed the clinical features, biological markers and clinical outcome of Japanese acute promyelocytic leukemia patients with or without ACAs who were treated by all-*trans* retinoic acid (ATRA) and chemotherapy, and tried to determine the role of ACAs on a 10-year follow up.

Adult patients with previously untreated *de novo* acute promyelocytic leukemia were registered consecutively into the JALSG APL97 study.[4] This study was approved by the institutional review boards of each participating institution and registered at *http://www.umin.ac.jp/ctrj/* under C000000206. Informed consent was obtained from patients before registration in the study in accordance with the Declaration of Helsinki.

Chromosomes analyzed by G-banding on bone marrow samples from patients before treatment were classified according to the 1995 International System for Human Cytogenetic Nomenclature (ISCN). Patients were categorized into two groups: those with t(15;17) and ACAs, and those with t(15;17) but without ACAs. Patients with der(17)t(15;17), der(15)t(15;17) or three-way translocation were placed in the group with ACAs.

Details of treatment protocol have been described previously.[4] In brief, remission induction consisted of ATRA and chemotherapy including idarubicin and cytarabine. Dose and duration of chemotherapy were based on initial leukocyte count. After completion of consolidation chemotherapy, patients negative for the *PML-RARA* tran-

**Table 1. Clinical features of patients.**

| Parameters | Total N.(%) | Total Median (range) | t(15;17) N.(%) | t(15;17) Median (range) | t(15;17) with ACAs N.(%) | t(15;17) with ACAs Median (range) | P |
|---|---|---|---|---|---|---|---|
| N. of patients | 225 | | 158 | | 67 | | |
| Age, years | | 48 (15-70) | | 49 (15-70) | | 45 (19-70) | 0.08 |
| 15-29 | 39 (17%) | | 21 (13%) | | 18 (27%) | | |
| 30-49 | 84 (37%) | | 62 (39%) | | 22 (33%) | | 0.06 |
| 50-70 | 102 (46%) | | 75 (48%) | | 27 (40%) | | |
| Gender | | | | | | | 0.24 |
| Male | 122 (54%) | | 90 (57%) | | 32 (48%) | | |
| Female | 103 (46%) | | 68 (43%) | | 35 (52%) | | |
| Leukocyte count, $\times 10^9$/L | | 1.7 (0.03-256) | | 1.65 (0.03-256) | | 1.7 (0.4-70.9) | 0.77 |
| Less than 3.0 | 135 (60%) | | 93 (59%) | | 42 (63%) | | |
| 3.0-10.0 | 48 (21%) | | 31 (20%) | | 17 (26%) | | 0.21 |
| 10.0 or higher | 42 (19%) | | 34 (21%) | | 8 (12%) | | |
| Platelet count, $\times 10^9$/L | | 29 (2-238) | | 30 (2-238) | | 29 (3-180) | 0.69 |
| Less than 10 | 31 (14%) | | 26 (16%) | | 5 (7.4%) | | |
| 10-40 | 10 (48%) | | 71 (45%) | | 38 (57%) | | 0.12 |
| 40 or higher | 85 (38%) | | 61 (39%) | | 24 (36%) | | |
| DIC score* | n = 213 | 6 (0-12) | n = 151 | 6 (0-12) | n = 62 | 6 (0-11) | 0.46 |
| 3 or higher | 198 | | 139 (92%) | | 59 (95%) | | |
| 10 or higher | 12 | | 16 (11%) | | 5 (8%) | | |
| FAB subtype | | | | | | | 0.04 |
| Typical | 210 (93%) | | 144 (91%) | | 66 (99%) | | |
| Variant | 15 (7%) | | 14 (9%) | | 1 (1%) | | |
| CD56 expression | n = 192 | | n = 128 | | n = 64 | | 0.45 |
| positive | 19 (10%) | | 11 (9%) | | 8 (13%) | | |
| negative | 173 (90%) | | 117 (91%) | | 56 (87%) | | |
| Peripheral blood count, $\times 10^9$/L | | | | | | | |
| leukocyte < 10, platelet > 40 | 72 (32%) | | 51 (32%) | | 21 (31%) | | |
| leukocyte < 10, platelet < 40 | 112 (50%) | | 74 (47%) | | 38 (57%) | | 0.22 |
| leukocyte > 10 | 41 (18%) | | 33 (21%) | | 8 (12%) | | |
| Incidence of secondary | | | | | | | |
| MDS/AML | 5 (2%) | | 4 (3%) | | 1 (1%) | | 0.63 |

*FAB: French-American-British; EFS: event free survival; RFS: relapse free survival. NA: not applicable; *DIC score, Score 3 indicates suspected DIC; scores from 4 to 10, definitive DIC; score 10 or more, severe DIC.*

script were randomly allocated either to receive 6 courses of intensified maintenance chemotherapy or to observation. Patients who were positive for the *PML-RARA* fusion transcript received late ATRA therapy followed by maintenance therapy, and received allogeneic hematopoietic stem cell transplantation if they had a human leukocyte antigen-identical donor.

Hematologic response was evaluated by standard criteria according to a previous report.[2] Hematologic and molecular relapse detected by RT-PCR analysis of *PML-RARA* was considered a relapse event.

The primary end point of the JALSG APL97 study was overall survival and disease free survival of patients who achieved complete remission. Overall survival for all patients was calculated from the first day of therapy to death or last visit. Disease free survival was measured from the date of complete remission to relapse, death from any cause or last visit. We also evaluated overall and disease free survival from the time of randomization to maintenance chemotherapy or observation.

Clinical and biological characteristics were compared between patients with or without ACAs by the $\chi^2$ test or Fisher's exact test for categorical data, and Wilcoxon's rank-sum test for continuous data. Overall and disease free survival were estimated by the Kaplan-Meier method and then compared by the log rank test. Clinical outcomes were updated on January 2009 and the median follow-up period is 7.3 years. Statistical analyses were performed using SPSS 11.0 software (SPSS Inc, Chicago, IL, USA).

Among 302 patients enrolled between May 1997 and June 2002, 283 patients were evaluable.[4] Of these, 58 patients were excluded because of insufficient data for ACAs status. Thus, the present analysis was carried out on 225 patients.

Sixty-seven (30%) of 225 patients had ACAs. Trisomy 8 was the most frequently observed ACA and detected in 21 cases (31%). Seven cases (11%) had ACAs in chromosome 15 in addition to t(15;17), 6 (9%) in chromosome 9, 6 (9%) in chromosome 7, 4 (6%) in chromosome 15, and 4 (6%) in chromosome 6. There was no significant difference in clinical or biological characteristics between the two groups, except the frequency of M3v (1% *vs.* 9%, *P*=0.04) (Table 1).

Complete remission rates in patients with or without ACAs were 97% and 95%, respectively (*P*=0.72). There was no difference in cumulative incidence of early death at 50 days, severe hemorrhagic complication or retinoic acid syndrome between the two groups (*P*=0.16, *P*=0.46 and *P*=0.16, respectively). There was also no difference in overall survival, disease free survival or cumulative incidence of relapse between the two groups (91% *vs.* 84%, *P*=0.18; 68% *vs.* 71%, *P*=0.59; 26% *vs.* 22%, *P*=0.51, respectively). Overall and disease free survival are shown in Figure 1A and B. In addition, clinical outcome was analyzed among subgroups of patients with ACAs. However, ACAs including chromosome 8, 7, 9, 15 and 17 did not influence outcomes.

Clinical and biological characteristics have been compared between patients with or without ACAs. ACAs have been detected in 26% to 33% of newly diagnosed acute promyelocytic leukemia patients in whom trisomy 8 was consistently the most frequent ACA.[5-9] In this study, 67 patients (30%) had ACAs, and trisomy 8 was the most frequent (31%). There was no significant difference in overall survival, disease free survival or relapse rate between patients with or without trisomy 8.

The frequency of M3v was significantly lower among our patients with ACAs. This agrees with the report by Schoch *et al.*,[10] although several previous studies showed that the morphology of M3v was not related to the presence of ACAs.[5,6,8] The inconsistency of these results may be caused by a considerably smaller number of M3v cases (16% to 27% of APL). Some authors have reported that the morphology of M3v is related to fms-like tyrosine kinase 3 mutations.[8,11,12] Future analysis of this with ACAs is needed.

Several authors have discussed the clinical importance of ACAs in acute promyelocytic leukemia patients treated with ATRA and chemotherapy. Cervera *et al.*[9] found in the LPA99 trial that ACAs were associated with lower relapse free survival in univariate analysis but not in mul-

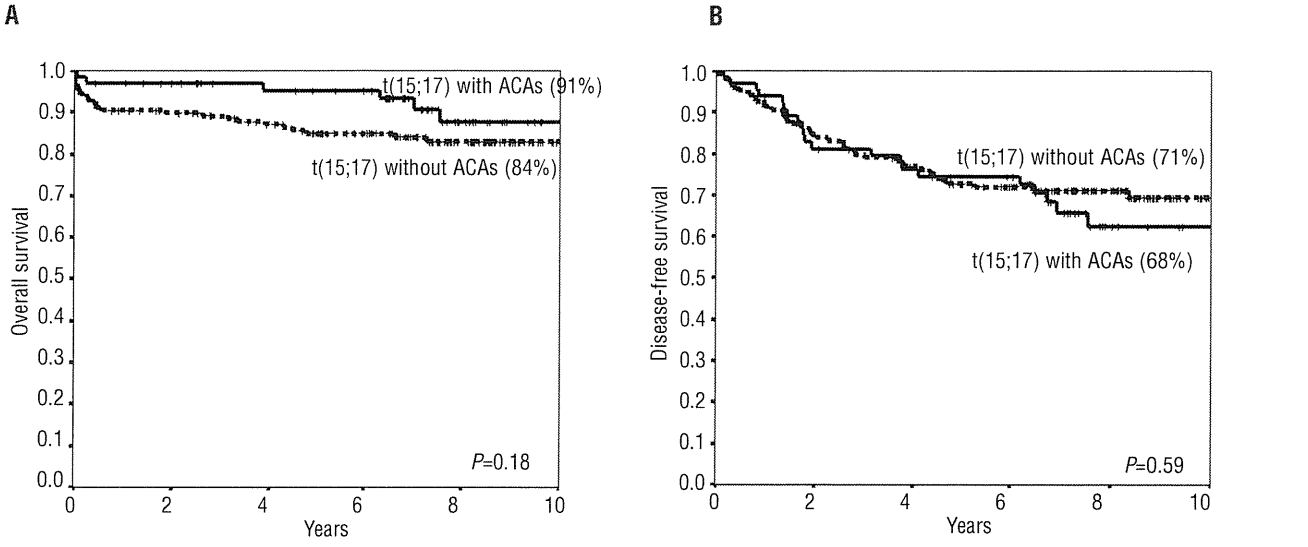


Figure 1. Overall survival and disease free survival of APL patients between with or without additional chromosomal abnormalities in addition to t(15;17). (A) Overall survival (91% *vs.* 84% at 10 years, *P*=0.18), (B) Disease-free survival (68% *versus* 71% at 10 years, *P*=0.59) were similar between two groups.

tivariate analysis. Schlenk *et al.*[8] analyzed 82 patients and reported that ACAs were an unfavorable prognostic marker for overall survival due to early death during the induction therapy. On the contrary, Botton *et al.*[6] and Hernandez *et al.*[7] reported that ACAs had no impact on clinical outcome. In our study, ACAs also did not show any prognostic significance. One of the reasons for this discrepancy would be that the clinical outcome of acute promyelocytic leukemia has recently improved dramatically. The outcome of each subgroup has also been greatly improved, although with some limitations, because patients have been stratified according to risk factors and consequently recent studies have used risk-adapted therapies. Thus, it may become more difficult to identify prognostic factors in acute promyelocytic leukemia.

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ORIGINAL ARTICLE

# A decision analysis of allogeneic hematopoietic stem cell transplantation in adult patients with Philadelphia chromosome-negative acute lymphoblastic leukemia in first remission who have an HLA-matched sibling donor

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**Clinical studies using genetic randomization cannot accurately answer whether adult patients with Philadelphia chromosome-negative acute lymphoblastic leukemia (ALL) who have a human leukocyte antigen (HLA)-matched sibling should undergo allogeneic hematopoietic stem cell transplantation (HSCT) or chemotherapy in first remission, as, in these studies, patients without a sibling donor undergo alternative donor transplantation or chemotherapy alone after a relapse. Therefore, we performed a decision analysis to identify the optimal strategy in this setting. Transition probabilities and utilities were estimated from prospective studies of the Japan Adult Leukemia Study Group, the database of the Japan Society for Hematopoietic Cell Transplantation and the literature. The primary outcome measure was the 10-year survival probability with or without quality of life (QOL) adjustments. Subgroup analyses were performed according to risk stratification on the basis of white blood cell count and cytogenetics, and according to age stratification. In analyses without QOL adjustments, allogeneic HSCT in first remission was superior in the whole population (48.3 vs 32.6%) and in all subgroups. With QOL adjustments, a similar tendency was conserved (44.9 vs 31.7% in the whole population). To improve the probability of long-term survival, allogeneic HSCT in first remission is recommended for patients who have an HLA-matched sibling.**

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## Introduction

With modern intensive chemotherapy, 74–93% of adult patients with acute lymphoblastic leukemia (ALL) achieve complete remission. However, the overall survival rate is only 27–48% because of the high rate of relapse.[1] Therefore, the establishment of optimal postremission therapy is important. The efficacy of allogeneic hematopoietic stem cell transplantation (HSCT) for adult patients with ALL in first remission has been demonstrated through clinical studies using genetic randomization, in which patients with a human leukocyte antigen (HLA)-matched sibling donor were allocated to the allogeneic HSCT arm, and those without a donor were placed in the chemotherapy or autologous transplantation arm. First, the LALA-87 trial showed that overall survival in patients with a donor was better than that in patients without a donor in a subgroup analysis of patients with high-risk characteristics.[2] A meta-analysis of seven similar studies confirmed that the donor group was superior to the non-donor group in patients with high-risk ALL in first remission.[3] However, such genetic randomization studies cannot accurately answer the question of whether patients with an HLA-matched sibling should undergo allogeneic HSCT or chemotherapy in first remission. In these studies, patients without a sibling donor had to choose transplantation from an alternative donor or chemotherapy alone once they had a relapse. The outcome of these treatments has been reported to be inferior to that of HSCT from an HLA-matched sibling donor in patients with relapsed ALL; therefore, the expected survival after the decision to continue chemotherapy in first remission in patients without a sibling donor is assumed to be originally poorer than that in patients with a sibling donor. However, it is practically difficult to perform a clinical trial in which patients with an HLA-matched sibling in first remission are randomly assigned to receive allogeneic HSCT or chemotherapy alone. Another important problem has been poor compliance with the assigned treatment in some studies. In addition, previous genetic

randomization studies did not consider the quality of life (QOL), especially that associated with graft-versus-host disease (GVHD). Therefore, we performed a decision analysis incorporating QOL adjustments using a decision tree based on the results of Japan Adult Leukemia Study Group (JALSG) prospective studies (ALL93[4] and ALL97[5]), the database of the Japan Society for Hematopoietic Cell Transplantation (JSHCT)[6] and literature. Patients with Philadelphia chromosome (Ph)-positive ALL were not included in our analysis because the outcome of treatment in these patients has improved dramatically since tyrosine kinase inhibitors became available.[7]

Recently, the Medical Research Council/Eastern Cooperative Oncology Group (MRC/ECOG) trial demonstrated the efficacy of allogeneic HSCT in ALL patients and in standard-risk patients, but not in high-risk patients,[8] which was inconsistent with previous studies. This difference might partly depend on the definition of high-risk patients. In the MRC/ECOG study, an age of higher than 35 years was considered to be a high-risk factor. Therefore, we performed separate subgroup analyses according to risk stratification on the basis of white blood cell count and cytogenetics, and according to age stratification with a cutoff of 35 years.

## Methods

### *Model structure*

We constructed a decision tree (Figure 1) to identify the optimal treatment strategy for adult patients with Ph-negative ALL in first remission who have an HLA-matched sibling.[9,10] The square at the left represents a decision node. We can decide to either proceed to allogeneic HSCT or continue chemotherapy in first remission. We did not include a decision to perform autologous HSCT, as autologous HSCT has not been shown to be superior to chemotherapy alone in a meta-analysis.[3] Circles, called chance nodes, follow each decision, and each chance node has two or three possible outcomes with a specific probability called the transition probability (TP). Every branch finally ends with triangles, called terminal nodes, and each terminal node has an assigned payoff value, called utility, according to different health states. Calculations were performed backward, from right to left in the decision tree. The sum of the products of TPs and utilities of the branches becomes the expected value for each chance node, and eventually the sum of the expected values in all of the chance nodes following the decision nodes becomes the expected value of each decision. The following analyses were performed using TreeAge Pro 2009 software (Williamstown, MA, USA). This study was approved by the Committee for Nationwide Survey Data Management of JSHCT, and the Institutional Review Board of Jichi Medical University.

### *Data sources*

Outcomes after continuing chemotherapy in first remission were estimated from JASLG studies (ALL93 and ALL97). Patients with Ph-negative ALL, aged 15–54 years, were included, and those who never achieved remission with chemotherapy were excluded. Data from 122 patients in ALL93 and 119 patients from ALL97 were analyzed separately, and then combined by weighting the number of patients. Outcomes after allogeneic HSCT in various disease statuses were estimated from the database of the JSHCT. Patients with Ph-negative ALL, aged 16–54 years, who underwent a first myeloablative allogeneic HSCT from a serologically HLA-A, -B, -DR loci-matched sibling between 1993 and 2007 were included. Of them, 408, 61, 14 and 94 patients were in first remission, second remission, third or later remission and non-remission, respectively, at allogeneic HSCT.

The characteristics of the patients included in this study are summarized in Table 1. There was no significant difference in their baseline characteristics. To determine the following TPs,

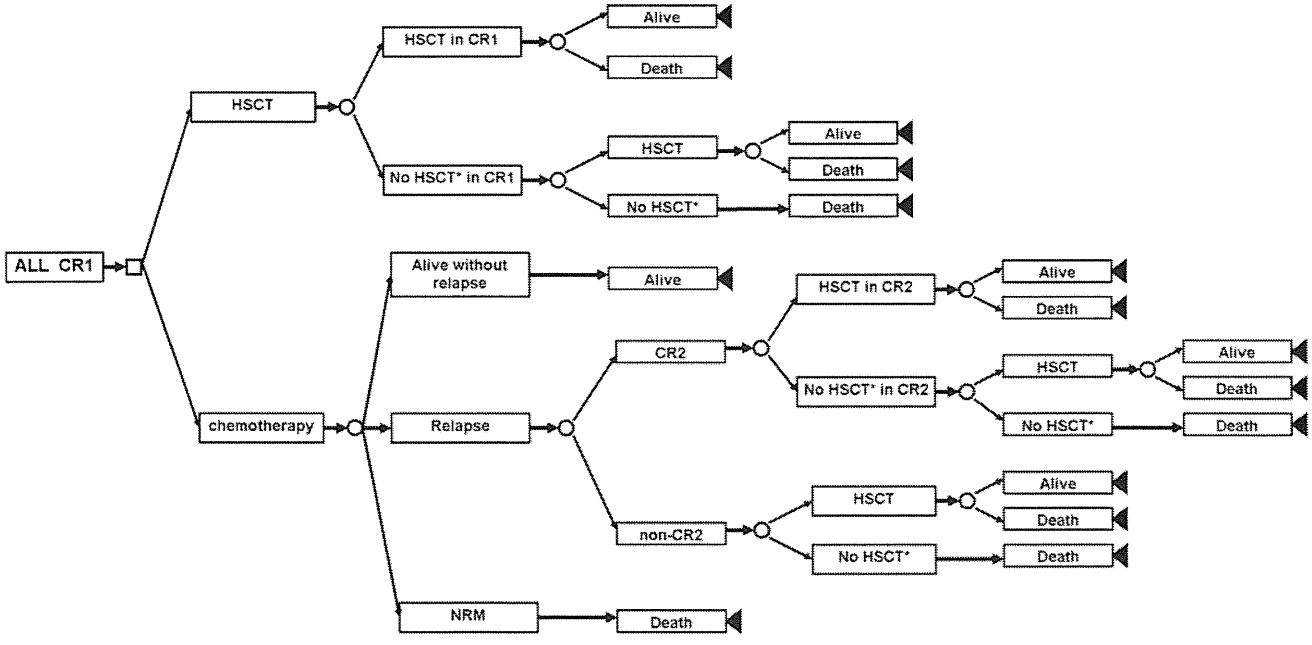


**Figure 1** Decision tree used in this study. Decision analysis was performed on the basis of a decision tree. A square indicates a decision node and open circles indicate chance nodes. In analyses with a QOL adjustment, 'Alive' after transplantation was followed by two branches with or without active chronic GVHD. *HSCT was not performed because of early relapse, death and so on. ALL, acute lymphoblastic leukemia; CR, complete remission; NRM, non-relapse mortality.

**Table 1** Patient characteristics in the three data sources

| | *Chemotherapy in CR1* | | *HSCT in CR1* | P[a] |
|---|---|---|---|---|
| | *JALSG ALL93* | *JALSG ALL97* | *JSHCT* | |
| No. of patients | 122 | 119 | 408 | |
| Median age (range) | 26 (15–54) | 26 (15–54) | 29 (16–54) | 0.72 |
| No. of males/females | 72/50 | 54/65 | 230/178 | 0.06 |
| Median WBC count at diagnosis (range) ( $\times 10^9$/l) | 9.5 (0.6–468.0) | 10.2 (0.3–398.0) | 10.4 (0.4–801.0) | 0.91 |
| Karyotype standard:high[b], ratio | 20:1 | 30:1 | 15.4:1 | 0.55 |

Abbreviations: CR, complete remission; HSCT, hematopoietic stem cell transplantation; JALSG, Japan Adult Leukemia Study Group; JSHCT, Japan Society for Hematopoietic Cell Transplantation; WBC, white blood cell.
[a]Statistical analyses were performed using the Kruskal–Wallis test for continuous variables and the $\chi^2$-test for categorical variables.
[b]t(4;11) and t(1;19) were classified as high-risk karyotypes, and other karyotypes were classified as standard risk.

overall survival and leukemia-free survival (LFS) with a 95% confidence interval (CI) were calculated using the Kaplan–Meier method, whereas the cumulative incidences of non-relapse mortality and relapse with 95% CI were calculated using Gray's method,[11] considering each other as a competing risk. Probabilities that we could not estimate from these data were estimated from the literature.

### *Transition probabilities (TPs) and utilities*

TPs of the whole population were determined as summarized in Table 2. Each TP has a baseline value and a plausible range. Baseline decision analyses were performed on the basis of baseline values.

Patients may have been precluded from undergoing allogeneic HSCT because of early relapse or comorbidities even if they decided to undergo allogeneic HSCT, and therefore the TP of actually undergoing allogeneic HSCT in first remission after the decision branch to undergo allogeneic HSCT was determined as follows: first, the median duration between the achievement of first remission and HSCT without relapse was calculated as 152 days on the basis of JSHCT data. Next, LFS rates at 152 days after achieving first remission were calculated using the data of all patients who achieved remission in the JALSG studies, and the combined LFS was 0.80 (95% CI: 0.76–0.85). We considered this to be the TP for actually receiving HSCT in first remission, and assigned a baseline value of 0.80 and 95% CI to the plausible range. Similarly, patients may be precluded from undergoing allogeneic HSCT even though they have achieved second remission after they had a relapse of leukemia following a decision to continue chemotherapy. This TP of undergoing allogeneic HSCT in second remission could not be calculated from our data. We assigned a plausible range of 0.5–0.80; the former value was the only available rate in a large study[12] and the latter was the TP calculated above. The median of this range was taken as the baseline value. Probabilities regarding the actual rate of receiving HSCT in other disease statuses could not be obtained, even in the literature. Therefore, a baseline value of 0.5 was assigned with a wide plausible range of 0.3–0.7, although these values may not be closely related to the final expected value, as the probability of survival after receiving HSCT in these situations was extremely low. The TPs of 'Alive at 10 years' following HSCT in various disease statuses were determined on the basis of the JSHCT database. We assigned 95% CI to the plausible ranges.

The TPs of 'Alive without relapse at 10 years' and non-relapse mortality following chemotherapy in first remission were determined on the basis of JALSG studies, and the TP of relapse following chemotherapy was determined by subtracting the sum of these TPs from 1. The TP of achieving second remission after relapse in patients who decided not to undergo allogeneic HSCT in first remission was estimated to have a baseline value of 0.4, with a plausible range of 0.3–0.5 based on the literature.[12–14]

The primary outcome measure was the 10-year survival probability as described in the Discussion. The survival curve nearly reaches a plateau after 5 years and therefore 'Alive at 10 years' reflects 'Cure of leukemia', which is the primary goal of allogeneic HSCT. First, we considered only two kinds of health states, 'Alive at 10 years' and 'Dead', and assigned utility values of 100 to the former and 0 to the latter without considering QOL. Next, we performed a decision analysis while adjusting for QOL. 'Alive after chemotherapy without relapse at 10 years', 'Alive with active GVHD at 10 years' and 'Alive without active GVHD at 10 years' were considered as different health states. The proportion of patients with active GVHD among those who

**Table 2** Transition probabilities of the whole population

| | *Baseline value (plausible range)* |
|---|---|
| HSCT in CR1 | 0.80 (0.76–0.85) |
| Alive at 10 years following HSCT in CR1 | 0.57 (0.52–0.63) |
| HSCT after failure of HSCT in CR1 | 0.5 (0.3–0.7) |
| Alive at 10 years following HSCT after failure of HSCT in CR1[a] | 0.27 (0.16–0.38) |
| Alive at 10 years without relapse following CTx | 0.21 (0.15–0.28) |
| NRM at 10 years following CTx | 0.07 (0.04–0.10) |
| Achievement of CR2 after relapse following CTx | 0.4 (0.3–0.5) |
| HSCT in CR2 | 0.66 (0.5–0.80) |
| Alive at 10 years following HSCT in CR2 | 0.38 (0.27–0.53) |
| HSCT after failure of HSCT in CR2 | 0.5 (0.3–0.7) |
| Alive at 10 years following HSCT after failure of HSCT in CR2[b] | 0.18 (0.16–0.2) |
| HSCT in non-CR after relapse following CTx | 0.5 (0.3–0.7) |
| Alive at 10 years following HSCT in non-CR after relapse | 0.16 (0.1–0.27) |
| Rate of active GVHD at 10 years[c] | 0.18 (0.1–0.25) |

Abbreviations: CR, complete remission; CTx, chemotherapy; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; NRM, non-relapse mortality.
[a]This rate was estimated from the survival rate following HSCT in CR2 and HSCT in non-CR.
[b]This rate was estimated from the survival rate following HSCT in CR3 or more and HSCT in non-CR.
[c]The same baseline value and plausible range were used as the rate of active GVHD at 10 years following HSCT in various disease statuses, but one-way sensitivity analyses were performed separately in each status.