Low-dose Cytarabine plus Aclarubicin for Patients with Previously Untreated Acute Myeloid Leukemia or High-risk Myelodysplastic Syndrome Ineligible for Standard-dose Cytarabine plus Anthracycline

TOSHIHIRO FUKUSHIMA[1], HIROSHI KAWABATA[2], TOSHIOKI SAWAKI[1], TOMOMI SATOH[1], TAKUJI NAKAMURA[1], HARUKA IWAO[1], AKIO NAKAJIMA[1], TOMOYUKI SAKAI[1], MIYUKI MIKI[1], YOSHIMASA FUJITA[1], MASAO TANAKA[1], TAKAFUMI KAWANAMI[1], YASUFUMI MASAKI[1], TOSHIRO OKAZAKI[1] and HISANORI UMEHARA[1]

[1]*Department of Hematology and Immunology, Kanazawa Medical University, Ishikawa, Japan;*
[2]*Department of Hematology and Oncology, Graduate School of Medicine, Kyoto University, Kyoto, Japan*

Abstract. *Background: In order to assess the role of the combination of low-dose cytarabine (Ara-C) plus aclarubicin (CA) in remission induction for patients with untreated acute myeloid leukemia (AML) or high-risk myelodysplastic syndrome (MDS), we retrospectively analyzed the efficacy and safety of CA. Patients and Methods: Data of twenty patients with untreated AML or high-risk MDS who were ineligible for standard-dose Ara-C plus anthracycline and received CA as remission-induction therapy were analyzed. CA consisted of low-dose Ara-C (10 mg/m^2, subcutaneous injection every 12 hours, for 14 days) and aclarubicin (14 mg/m^2 for patients <70 years old and 10 mg/m^2 for patients ≥70 years old in a one-hour infusion for 4 days). Granulocyte colony-stimulating factor (G-CSF) was used from day 1 of CA to white blood cell count (WBC) recovery, except for patients with initial WBC of more than 20.0×10^3/mm^3. Results: Eleven patients (55%) achieved complete remission. All four patients whose WBC were ≥20.0×10^3/mm^3 and did not receive G-CSF were refractory to CA. The predicted 2-year overall survival rate and median survival duration of all 20 patients were 37.9% and 363 days, respectively. The predicted 1-year relapse-free survival (RFS) rate and median duration of RFS of 11 patients who achieved complete remission were 30.3% and 332 days, respectively. Only one patient died due to transfusion-related acute lung injury. No patients died due to severe infections. Conclusion: CA combination with G-CSF as remission-induction therapy is promising and well-tolerated in patients with previously untreated AML or high-risk MDS who are ineligible for standard-dose Ara-C plus anthracycline without leukocytosis. In order to improve RFS, intensive postremission chemotherapy or allogeneic hematopoietic stem cell transplantation should be introduced.*

Correspondence to: Toshihiro Fukushima, MD, Ph.D., Department of Hematology and Immunology, Kanazawa Medical University, 1-1 Daigaku, Uchinada, Ishikawa 920-0293, Japan. Tel: +81 762862211, Fax: +81 762869290, e-mail: tfukus@kanazawa-med.ac.jp

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Combination of standard-dose cytarabine (Ara-C) plus daunorubicin or idarubicin, named 3+7, is the standard remission-induction therapy for untreated acute myeloid leukemia (AML). The complete remission (CR) rate is approximately 60% to 80% in newly diagnosed younger adult patients with AML treated with 3+7 (1, 2). On the other hand, there are many patients ineligible for 3+7, because of poor performance status (PS), insufficient organ function, severe infection, or hypoplastic marrow. Many elderly patients are also ineligible for 3+7, or intensive chemotherapy, *i.e.* high-dose Ara-C because of a low CR rate, short response duration, and therapy-related mortality (3, 4). Remission-induction therapy for these patients has not been established. Standard therapies should be established based on large-scale prospective clinical trials, which exclude these patients. Accordingly, it is worth evaluating the efficacy and safety of the chemotherapy for these patients retrospectively. The CAG regimen, a combination of low-dose Ara-C, aclarubicin and granulocyte colony-stimulating factor (G-CSF), was proposed for patients with relapsed or refractory AML (5). A high response rate and good tolerability of CAG, not in cases of relapsed or refractory disease, but also for untreated elderly patients have been previously reported (6-10). In our institute, patients with

untreated AML or high-risk myelodysplastic syndrome (MDS) who were ineligible for 3+7 have been treated with low-dose Ara-C plus aclarubicin therapy (CA) as remission-induction therapy since 2000. Here, we retrospectively analyzed the efficacy and safety of CA to assess its role in remission induction for untreated AML and high-risk MDS.

Patients and Methods

Patients. We retrospectively analyzed the medical records of 20 patients with untreated AML or high-risk MDS who began CA as the remission-induction therapy at Kanazawa Medical University Hospital between July 2000 and February 2010. AML was diagnosed by the French-American-British (FAB) classification. All 20 patients were ineligible for 3+7 for various reasons.

Treatment. CA consisted of low-dose Ara-C (10 mg/m^2, subcutaneous injection every 12 hours, for 14 days) and aclarubicin (14 mg/m^2 for patients <70 years old and 10 mg/m^2 for patients ≥70 years old in a one-hour infusion for 4 days). G-CSF (filgrastim 75 or 150 μg or lenograstim 100 or 250 μg, subcutaneous injection) was used from day 1 of CA to white blood cell count (WBC) recovery except for patients with initial WBC of more than 20.0×10^3/mm^3. Patients who achieved CR received various postremission therapies according to their general condition. Sufficient supportive care, including prophylactic antibacterial or antifungal agents, was given if indicated.

Assessments. CR was defined as the presence of all of the following: fewer than 5% blasts in the bone marrow, no leukemia blasts in the peripheral blood, recovery of peripheral neutrophil counts to over 1.0×10^3/mm^3, and platelets (PLT) to over 100×10^3/mm^3. Relapse was defined as the presence of at least one of the following: recurrence of more than 10% leukemia cells in the bone marrow, any leukemia cells in the peripheral blood, and the appearance of extramedullary leukemia. Overall survival (OS) and relapse-free survival (RFS) were calculated from the first day of CA to death and from the day of the first CR to the day of the first relapse, respectively. Adverse events associated with the first course were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 2.0 (11).

Statistical analysis. Fisher's exact test was used in order to detect the factors that influenced the CR rate. Time-to-event analysis was performed according to the Kaplan–Meier method, and the log-rank test was applied to assess differences between subgroups. $p<0.05$ was considered significant.

Results

Patients' characteristics. Table I shows the characteristics of the 20 patients. The median age was 76 years (range 57-81 years). Seventeen patients were ≥70 years old. The number of patients belonging to FAB classification subgroups: refractory anemia with excess blasts (RAEB), RAEB in transformation, M0, M1, M2, M4 were 2, 2, 1, 5, 7, and 3, respectively. Ten out of 16 cases of AML were considered to have arisen from MDS. Karyotype analyses were available for all patients: one was classified into the favorable risk group, 15 into the intermediate risk group, and four into the adverse risk group according to the Medical Research Council classification (12). Eastern Cooperative Oncology Group PS of all patients was ≥2, including PS 3 in nine patients and PS 4 in one patient. The main reasons for patient ineligibility for 3+7 were age (≥75 years old, n=10), poor PS (n=5), hypoplastic marrow (n=3), severe infection (n=1) and arrhythmia (n=1). Sixteen patients received CA combination with G-CSF (CAG).

Response to CA. Eleven patients (55%) achieved CR; seven by one course and four by two courses. The median period to achieve CR was 34 days (range 28-75 days). One patient died on day 25 due to transfusion-related acute lung injury after packed red cell transfusion. Eight patients were refractory to CA. All four patients whose WBC were ≥20.0×10^3/mm^3 and who did not receive G-CSF were refractory to CA. WBC (<10.0×10^3/mm^3), PLT (≥50×10^3/mm^3) and the use of G-CSF were detected as favorable factors for CR rate (Table II). Among 11 patients who achieved CR, ten patients received consolidation therapy; eight received 1-3 courses of CAG, and two received 3 courses of standard intensity consolidation such as 3+7.

OS and RFS. The predicted 2-year OS rate and median survival duration of all 20 patients were 37.9% and 363 days, respectively (Figure 1). WBC (<10.0×10^3/mm^3), PLT (≥50×10^3/mm^3), favorable to intermediate risk karyotype, and the use of G-CSF were detected as favorable factors for OS (Table III). The predicted 1-year RFS rate and median duration of RFS of 11 patients who achieved CR were 30.3% and 332 days, respectively (Figure 2).

Adverse events. The median nadir of the neutrophil count and PLT during and after the first course of CA were 0.033×10^3/mm^3 (range 0-1.04×10^3/mm^3) and 13×10^3/mm^3 (range 0.3-55×10^3/mm^3), respectively. The median periods from initiation of CA to neutrophil recovery (≥0.5×10^3/mm^3) and PLT recovery (≥100×10^3/mm^3) were 21 days and 34 days, respectively. Table IV shows the non-hematological adverse events. The most frequent ≥grade 3 non-hematological adverse event was infection. Adverse events greater than grade 4 were not seen, except for one patient with transfusion-related acute lung injury.

Discussion

The recommended chemotherapy for elderly patients with AML or high-risk MDS is controversial. Kantarijian *et al*. analyzed 446 elderly patients with AML (age ≥70 years) treated with intensive chemotherapy, mainly with high-dose Ara-C. The CR rate was low (45%, excluding patients with a favorable karyotype) and 8-week mortality was very high

Table I. *Characteristics of patients (n=20).*

Characteristic	Value
Age (years)	
Median	76
Range	57-81
Gender (n)	
Male	12
Female	8
FAB classification subtype (n)	
Refractory anemia with excess blasts (RAEB)	2
RAEB in transformation	2
M0	1
M1	5
M2	7
M4	3
Hemoglobin (g/dl)	
Median	7.3
Range	4.0-12.4
White blood cell count ($\times 10^3/mm^3$)	
Median	2.87
Range	0.51-93.4
Blasts in peripheral blood (%)	
Median	8.0
Range	0-94.0
Platelet count ($\times 10^3/mm^3$)	
Median	47
Range	14-221
Cellularity of bone marrow (n)	
Hypocellular	4
Normocellular	4
Hypercellular	11
Unknown	1
Blasts in bone marrow (%)	
Median	33.3
Range	9.0-90.2
Infectious complication at diagnosis (n)	
Absent	12
Present	8

FAB classification, French-American-British classification.

Table II. *Impact of patients' characteristics on complete remission (CR) rate.*

	n	CR, n (%)	*p*-Value
Total	20	11 (55.0)	
Age			1.0000
<75 years	10	5 (50.0)	
≥75 years	10	6 (60.0)	
Gender			1.0000
Male	12	7 (58.3)	
Female	8	4 (50.0)	
MDS or arising from MDS			0.6424
No	6	4 (66.7)	
Yes	14	7 (50.0)	
Karyotype			0.2848
Favorable/intermediate risk	16	10 (62.5)	
Poor risk	4	1 (25.0)	
ECOG performance status			1.0000
2	10	6 (60.0)	
3,4	10	5 (50.0)	
Hemoglobin			0.6534
≥8.0 g/dl	9	4 (44.4)	
<8.0 g/dl	11	7 (63.6)	
White blood cell count			0.0081
$<10.0\times10^3/mm^3$	15	11 (73.3)	
$\geq10.0\times10^3/mm^3$	5	0 (0)	
Blasts in peripheral blood			0.2848
<50%	16	10 (62.5)	
≥50%	4	1 (25.0)	
Platelet count			0.0055
$\geq50\times10^3/mm^3$	10	9 (90.0)	
$<50\times10^3/mm^3$	10	2 (20.0)	
LDH			0.0703
<230 IU/l	7	6 (85.7)	
≥230	13	5 (38.5)	
Cellularity of bone marrow			0.0587
Hypo-normocellular	8	7 (87.5)	
Hypercellular	11	4 (36.4)	
Blasts in bone marrow			1.0000
<50%	12	7 (58.3)	
≥50%	8	4 (50.0)	
Infectious complication at diagnosis			1.0000
Absent	12	7 (58.3)	
Present	8	4 (50.0)	
Use of G-CSF			0.0260
Yes	16	11 (68.8)	
No	4	0 (0)	

ECOG, Eastern Cooperative Oncology Group; G-CSF, granulocyte colony-stimulating factor; MDS, myelodysplastic syndrome; LDH, lactate dehydrogenase.

(36%); the median survival duration was <6 months. They concluded that most elderly patients with AML, excluding patients with core binding factor leukemias and those without any of the four identified adverse risk factors for early death (age ≥80 years, complex karyotypes, PS ≥3, creatinine >1.3 mg/dl), were ineligible for high-dose Ara-C (13). Although the Dutch-Belgian Cooperative Trial Group for Hemato-Oncology and the Swiss Group for Clinical Cancer Research reported that an escalated dose of 90 mg/m^2 daunorubicin showed a higher CR rate compared with the standard dose of 45 mg/m^2 as remission-induction therapy for elderly patients (age ≥60 years) without additional toxic effects, there were no significant differences in event-free survival, disease-free survival and OS. Only patients who were 60 to 65 years had the greatest benefit from an escalated dose of daunorubicin in event-free survival, disease-free survival and OS (14). There are contrary reports regarding the efficacy of standard intensive remission-induction therapy such as 3+7. The Southwest Oncology Group reported that patients with poor PS and advanced age have a low CR rate and high risk of early death. The CR rate of patients aged ≥75 years was only 33%. Furthermore, 82%

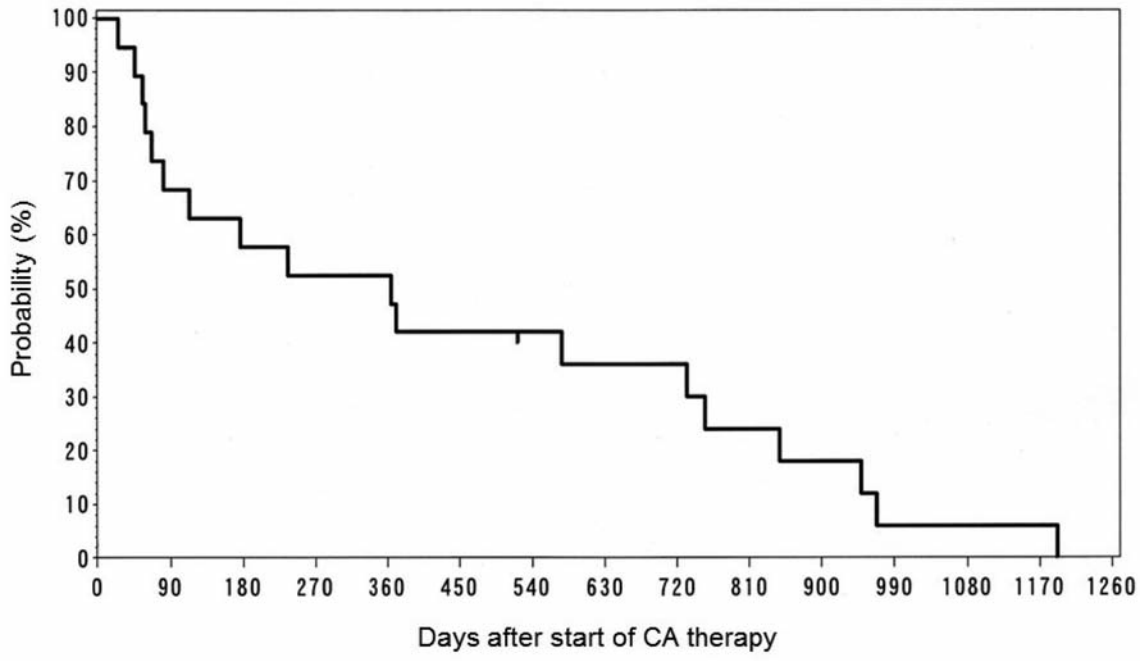

Figure 1. *Kaplan-Meier curve for overall survival of 20 patients treated with low-dose cytarabine plus aclarubicin (CA) therapy.*

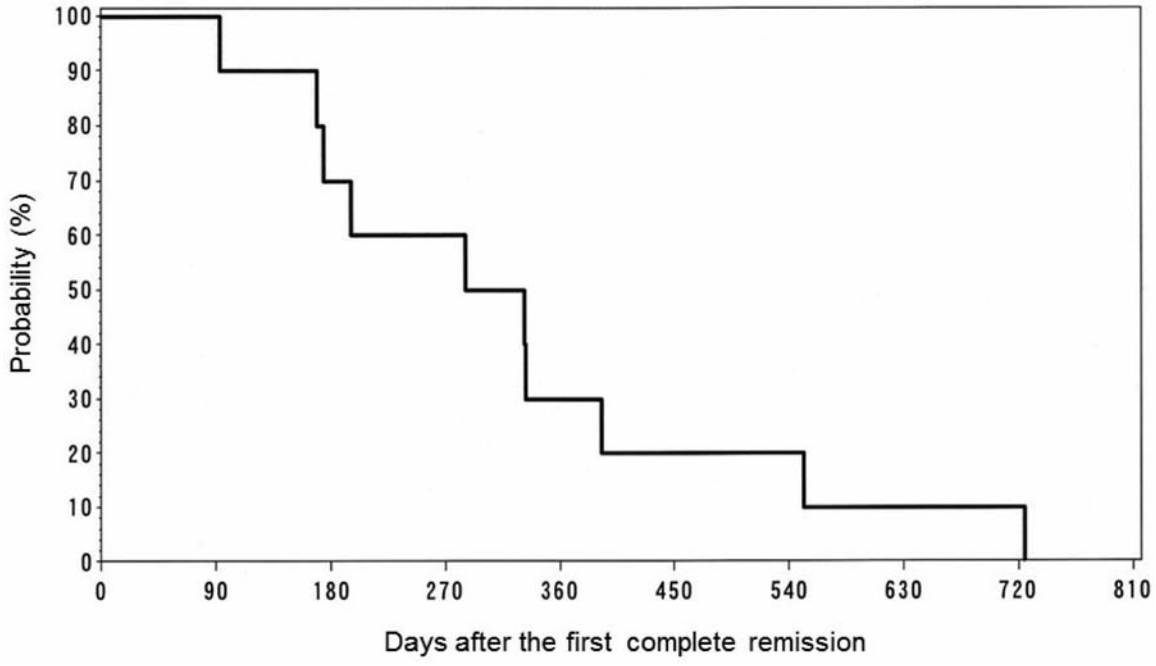

Figure 2. *Kaplan-Meier curve for relapse-free survival of 11 patients who achieved complete remission.*

of patients aged ≥75 years with PS 3 died within 30 days of the initiation of induction (15). The Gruppo Italiano Malattie Ematologiche dell'Adulto also reported that aggressive induction treatment for elderly patients appears to be very limited, except for a small subgroup of patients. Patients aged <70 years, with no heart disease, but WBC 10.0×10^3>/mm^3 had a significantly better survival when treated aggressively (16). On the other hand, the Swedish

Table III. *Impact of patients' characteristics on overall survival.*

	n	Median OS (days)	2-Year OS (%)	*p*-Value
Total	20	363	37.9	
Age				0.5165
<75 years	10	206	30.0	
≥75 years	10	576	46.7	
Gender				0.9198
Male	12	303	33.3	
Female	8	363	46.9	
MDS or arising from MDS				0.4802
No	6	370	20.8	
Yes	14	206	42.9	
Karyotype				0.0035
Favorable/intermediate risk	16	576	47.7	
Poor risk	4	62	0	
ECOG performance status				0.8378
2	10	303	30.0	
3,4	10	363	48.0	
Hemoglobin				0.5194
≥8.0 g/dl	9	176	44.4	
<8.0 g/dl	11	370	31.2	
White blood cell count				0.0156
$<10.0\times10^3/mm^3$	15	731	51.3	
$\geq10.0\times10^3/mm^3$	5	113	0	
Blasts in peripheral blood				0.2640
<50%	16	370	41.3	
≥50%	4	215	25.0	
Platelet count				0.0088
$\geq50.0\times10^3/mm^3$	10	754	66.7	
$<50.0\times10^3/mm^3$	10	74	10.0	
LDH				0.1393
<230 IU/l	7	731	51.4	
≥230	13	176	30.8	
Cellularity of bone marrow				0.3197
Hypo-normocellular	8	731	58.3	
Hypercellular	11	176	27.3	
Blasts in bone marrow				0.6217
<50%	12	303	33.3	
≥50%	8	363	46.9	
Infectious complication at diagnosis				0.4574
Absent	12	363	28.1	
Present	8	411	50.0	
Use of G-CSF				0.0371
Yes	16	576	47.7	
No	4	90	0	

ECOG, Eastern Cooperative Oncology Group; G-CSF, granulocyte colony-stimulating factor; MDS, myelodysplastic syndrome; LDH, lactate dehydrogenase.

Table IV. *Non-hematological adverse events during and after the first course of low-dose cytarabine and aclarubicin.*

	Grade				
Adverse event	1	2	3	4	5
Infection	0	0	17	0	0
Bleeding	0	0	0	0	0
Nausea/vomiting	7	3	5	0	0
Diarrhea	0	4	1	0	0
Mucositis	2	1	0	0	0
Alopecia	12	0	0	0	0
Other	1	3	0	0	1

Acute Myeloid Leukemia Registry Group reported that patients up to age 80 benefit from standard intensive treatment because 70% of them have PS 0-2 and standard intensive treatment reduces rather than increases the early death rate (17). Although the incidence of adverse events were low, the CR rate obtained by low-dose Ara-C was only 20-30% (18, 19). Supportive treatment or palliative chemotherapy is another strategy for elderly patients. Latagliata *et al*. retrospectively analyzed the survival of elderly patients ineligible for intensive chemotherapy who received supportive treatment, palliative chemotherapy, or low-dose Ara-C. The median survival duration of all patients was 178 days. The median survival durations of the patients who received only supportive treatment and of patients who needed additional chemotherapy were almost the same (201 days and 171 days, respectively) (20).

In clinical practice, younger patients with poor PS or severe comorbidities have received reduced intensity chemotherapy. A high response rate and good tolerability of CAG for elderly patients have been reported previously (5-10). In our institute, patients with untreated AML or high-risk MDS who were ineligible for standard intensity remission-induction therapy due to age, poor PS or severe comorbidities have been treated with CA as remission-induction therapy in order to obtain sufficient clinical efficacy and to reduce severe adverse events. The CR rate was favorable, with less severe adverse events. Only one patient died due to transfusion-related acute lung injury. No patients died due to severe infections.

On the other hand, RFS was not satisfactory. The predicted 1-year RFS rate and the median duration of RFS were only 30.3% and 332 days, respectively. In order to improve RFS, younger patients should receive intensive post-remission chemotherapy or allogeneic hematopoietic stem cell transplantation if they recover favorable PS and sufficient organ function (21). Reduced-intensity-conditioning hematopoietic stem cell transplantation should be considered because it is well tolerated with reasonable survival in elderly patients (22). Gemtuzumab ozogamicin, lenalidomide, and azacitidine are also candidates for postremission chemotherapy to improve RFS in elderly patients (23-25).

In conclusion, CAG as remission-induction therapy is promising and well tolerated for patients with previously

untreated AML or high-risk MDS who are ineligible for standard-dose Ara-C plus anthracycline without leukocytosis. To improve RFS, intensive postremission chemotherapy or allogeneic hematopoietic stem cell transplantation should be introduced if patients recover favorable PS and sufficient organ function.

Conflict of Interest

The Authors declare they have no conflicts of interest.

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