The Response to Induction Therapy Is Crucial for the Treatment Outcomes of Elderly Patients with Acute Myeloid Leukemia: Single-institution Experience

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Abstract. *Background/Aim: The prognosis of acute myeloid leukemia (AML) in elderly patients remains poor due to their poor general condition and the intrinsic chemotherapy-resistant nature of their leukemia cells. The present retrospective study evaluated the clinical background as well as the response to treatment, of an unselected group of elderly patients with AML who were admitted to our Institution over a period of six years. Patients and Methods: Patients aged 65 years or older with AML admitted to our Institution between January 2005 and May 2011 were evaluated retrospectively. Results: Forty-six patients were admitted to our Institution, among whom 41 received remission induction chemotherapy. Twenty-four patients received intensive chemotherapy, while 13 received low-dose cytarabine-based chemotherapy. Other modalities were used in four patients. Complete remission was obtained in 20 patients (48.8%). The complete remission rate (50.0%) tended to be higher in patients receiving intensive chemotherapy than in those receiving low-dose cytarabine-based regimens (30.7%; p=0.25). The median survival time for the whole patient group was 12 months and the 2-year overall survival was 18%. The median survival times for patients with complete remission and for non-responding patients were 14 months and 7 months, respectively. The 2-year overall survival in patients with complete remission was 32%, while that of non-responding patients was 6% (p=0.0025, log-rank test). Conclusion: The present study suggests the necessity of achieving complete remission for obtaining better survival for elderly patients with AML.*

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The treatment of acute myeloid leukemia (AML) has progressed greatly over the past 40 years (1-4). Approximately 70% complete remission (CR) and 40% long-term survival are obtained in patients under 60 years old. However, 5-year survival rates in elderly patients are only one third of those seen in younger ones (5-10).

The adverse prognostic impact of older age is attributable to differences in both disease-related factors and patient-related factors. The former include adverse chromosomal abnormalities, antecedent bone marrow failure, and the chemotherapy-resistant nature, such as multidrug resistance (11, 12). The latter are the limited tolerability these patients have for intensive chemotherapy due to their poor general condition, organ dysfunction, and comorbidities (8, 11). This background of AML in the elderly may thus ristrict the physicians' choice of treatments: best supportive care, low-intensity chemotherapy, or investigational agents rather than standard, intensive combination regimens (13, 14).

Patients with AML are predominantly elderly, with a median age at diagnosis of around 65 years. Improvement of therapeutic outcomes of older patients is, therefore, indispensable for a cure of AML. Herein, we retrospectively evaluated the clinical background, as well as the response to treatment, of an unselected group of elderly patients with AML who were admitted to our Institution over a period of six years.

Patients and Methods

Patients and diagnosis. Patients aged 65 years old or older who were admitted to the University Hospital of Fukui between January 2005 and May 2011 were considered for this study. The patients were all newly-diagnosed with AML (those with acute promyelocytic leukemia were excluded). To obtain the diagnosis, bone marrow samples were aspirated and evaluated using standard

techniques, including hemograms of May-Grünwald-Giemsa-stained smears, cell surface marker detection, and karyotyping. The classification of AML was made according to the French–American–British criteria (15).

Treatment and response criteria. The patients received one of the following therapies according to the treating physicians' choice: a '3+7' at regular or reduced doses, a low-dose cytarabine (ara-C)-based regimen, and other modalities including gemtuzumab ozogamicin, and investigational agents. Some patients received best supportive care without the administration of anticancer agents. The standard '3+7' induction chemotherapy consisted of continuous intravenous infusion of ara-C at 100 mg/m^2 on days 1-7 and 30-min intravenous infusion of idarubicin at 12 mg/m^2 on days 1-3 or daunorubicin at 50 mg/m^2 on days 1-5 for young adults (16). The doses of these agents were reduced according to the patient's background and physician's decision by 20-30%. Low-dose ara-C-based regimens included low-dose ara-C (10 mg/m^2 twice daily for 10-14 days) as a single agent (17), CAG regimen (ara-C at 10 mg/m^2 twice daily for 10-14 days, aclarubicin at 20 mg/m^2 for four days, granulocyte-colony stimulating factor for 10-14 days) (18), and AMA regimen (ara-C at 10 mg/m^2 twice daily, melphalan at 2 mg/body every other day, and mitoxantrone at 3 mg/m^2 every three days for 10-14 days) that had been developed in our previous trial (19).

CR was defined by the criteria of Cheson *et al*. as normalization of peripheral blood and bone marrow characteristics, including the disappearance of blasts, granulocyte counts at >1,000/μl and platelet counts at >100,000/μl in peripheral blood, as well as <5% blasts in the bone marrow (20). Other responses were considered as failures. When CR was achieved, 3-4 courses of post-remission chemotherapy were performed using the regimens similar to the remission induction treatment administered for each patient according to the physician's decision. After the completion of chemotherapy, the patients were discharged and their disease status was monitored periodically through physical examinations, blood tests, and bone marrow examinations. Those who did not achieve CR received either the salvage regimens or best supportive care without the use of anti-leukemic agents, depending on the patient's request and the physician's choices.

Statistical analyses. All statistical analyses and generation of graphs were performed using Microsoft Excel 2013 software (Microsoft, Redmond, WA, USA) and GraphPad Prism software (version 6.0) (GraphPad Software, Inc. San Diego, CA, USA). Values of $p<0.05$ were considered statistically significant.

Results

Patients' characteristics. Between January 2005 and May 2011, 46 patients with AML aged 65 years and older were admitted to our Institution. The characteristics of these patients are shown in Table I.

The median follow-up of this cohort was 9.5 months (range=0-86 months). Chromosomal analysis was performed successfully in 40 patients (89%). Four patients displayed a favorable karyotype (t(8;21)(q22;q22) or chromosome 16 abnormality). Twelve patients had an unfavorable karyotype (monosomies or deletions of chromosomes 5 and 7; abnormalities of the long arm of chromosome 3; or complex cytogenetic abnormalities) (21). Twenty four patients were classified into an intermediate-risk karyotypic group, among whom eight presented with a normal karyotype. The cluster of differentiation 34 (CD34) positivity and Wilms' tumor 1 (*WT1*) mRNA levels were determined, and no meaningful trends were found for either parameter in terms of age (Figure 1).

Table I. *Patient characteristics*.

	All patients	Chemotherapy administered
Total number	46	41
Median age (range)	75 (65-91)	74 (65-90)
Male/female	28:18	24 : 17
FAB		
M0	2	2
M1	2	2
M2	17	16
M4	5	5
M5	4	3
M6	2	2
M7	2	1
LT of MDS	10	8
LT of MPD	2	2

Patients were admitted in the University Hospital of Fukui between 2005-2012. AML, Acute myeloid leukemia; MDS, myelodysplastic syndrome; FAB, French-American-British classification; LT, leukemic transformation; MPD, myeloproliferative disease. Patients with acute promyelocytic leukemia were excluded.

Treatment. Among the 46 patients, 41 received remission induction chemotherapy (89.1%). Twenty-four patients received cytarabine-based intensive chemotherapy. The average dose reduction of anti-leukemic agents was 25% (range=0-50%). Thirteen patients received low-dose ara-C-based chemotherapy (low-dose ara-C for four patients, CAG for six patients, AMA for three patients). The other four patients underwent a phase I clinical study of an investigational agent or gemtuzumab ozogamicin. No patients underwent allogeneic stem cell transplantation.

Therapeutic outcomes. CR was obtained in 20 out of 41 patients (48.8%) after induction chemotherapy. Three patients died within 30 days from the initiation of the induction chemotherapy. The CR rates were comparable between the patients aged <75 years (10/20, 50%) and those aged ≥75 years (10/21, 47.6%) ($p=0.46$, Chi-square test; (Table II), (Figure 2A). However, the CR rate was apparently low in those aged ≥80 years (3/8, 37.5%; (Table II), (Figure 2A). The CR rate tended to be higher in the favorable-risk group than in the intermediate-risk group ($p=0.02$, Chi-square test) and than in the adverse-risk group ($p=0.02$, chi-

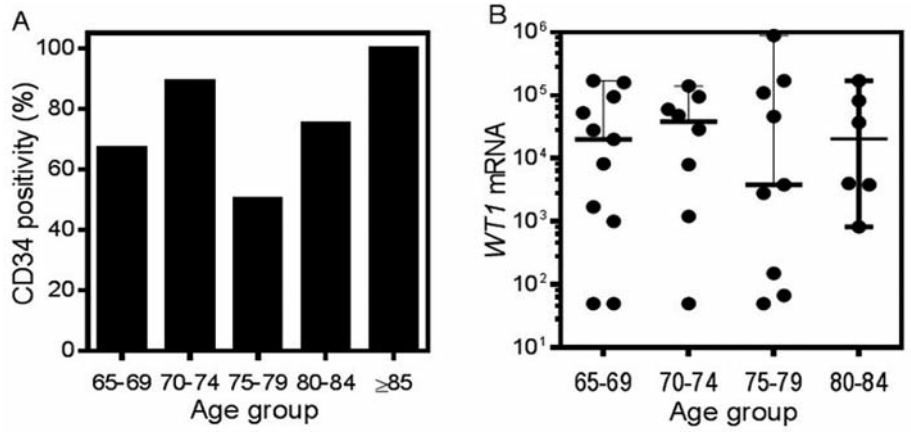

Figure 1. *Characterization of leukemia cells. (A) The cluster of differentiation 34 (CD34) positivity of leukemic cells. (B) Wilms' tumor 1 (WT1) transcript levels in peripheral blood.*

square test) (Table III), (Figure 2B). The CR rate tended to be higher in the patients receiving intensive chemotherapy than in those receiving low-dose ara-C-based regimens (p=0.25); (Table IV), (Figure 2C).

Survival curves were drawn according to the subgroups (Figure 3). The median survival time (MST) for the patients group overall was 12 months, and the 2-year overall survival (OS) was 18% (Figure 3A). The MSTs in patients with CR and non-responding patients were 14 months and 7 months, respectively, and their 2-year OSs were 32%, and 6%, respectively (Figure 3B). The difference in survival between the CR group and the non-CR group was significant (p=0.0025, log-rank test). The MSTs for the patients aged <75 years and ≥75 years were 14 months and 7 months, respectively, and the 2-year OSs in the patients aged <75 years and ≥75 were 13 % and 5 %, respectively (Figure 3C). The difference in survival between these two age groups was not significant (p=0.08, log-rank test). The MSTs for the favorable-, the intermediate-, and the adverse-risk groups were 13 months, 12 months, and 9 months, respectively, and the 2-year OSs in these groups were 50%, 23%, and 0%, respectively (Figure 3D). The difference in survival among these three groups was not significant (favorable- *vs*. intermediate-risk, p=0.18; favorable- *vs*. adverse-risk, p=0.06, intermediate- *vs*. adverse-risk, p=0.21, by log-rank test).

Discussion

The present study showed that long-term survivors accounted for fewer than 20% in the elderly AML cohort evaluated (Figure 3A), which is almost comparable to the results in other studies (6-8). Older age, adverse karyotype, and non-CR state appeared to be associated with poorer survival (Figure 3). Because the prognosis of elderly patients with

Table II. *Induction treatments according to age group.*

Age group (years)	All patients (number)	Patients receiving chemotherapy (number)	CR (number) (%)
65-69	12	11	4 (36.4)
70-74	9	9	6 (55.6)
75-79	14	13	7 (53.8)
80-84	9	7	3 (42.9)
≥85	2	1	0 (0)
Total	46	41	20 (48.8)

CR, Complete remission.

Table III. *Karyotypic findings and initial responses.*

Risk subgroups	CR/all (n)	CR rate (%)
Favorable	4/4	100.0
Intermediate	10/24	41.7
Adverse	6/12	50.0

CR, Complete remission.

Table IV. *Induction chemotherapies and initial responses.*

Regimens	CR/all (n)	CR rate (%)
Intensive chemotherapy	12/24	50.0
Low-dose ara-C-based	4/13	30.7
Other*	4/4	100

CR, Complete remission. *Other therapeutic modalities included an investigational agent and gemtuzumab ozogamicin.

AML is affected by age, disability, and comorbidity along with the characteristics of leukemia cells (13), patients' physical condition and intrinsic chemotherapy-resistant nature of leukemia cells should both be evaluated. The patient background should be taken into account because patients in good general condition might be able to undergo more potent remission induction chemotherapy. Nevertheless, the high intensity of chemotherapy does not overcome the intrinsic resistance of leukemia cells in all cases. In this regard, the selection of patients who would benefit from intensive chemotherapy is crucial (13) because the achievement of CR is indispensable for a better prognosis (Figure 3B) (22). Elderly patients with AML should thus be individualized considering the risk of induction death and the probability of achieving CR (5).

The Acute Leukemia French Association (ALFA) analyzed 416 elderly patients rink AML treated in the ALFA-9803 trial to derive a decision index (23). The authors proposed that those patients with unfavorable cytogenetics, as well as patients with at least two of the following features: age ≥75 years, performance status ≥2, and white blood cell count ≥50,000/μl, should not be considered for standard intensive chemotherapy (23). Kantarjian *et al*. investigated 446 patients with AML aged 70 years or more treated with ara-C-based intensive chemotherapy to identify risk groups for high induction (8-week) mortality. A multivariate analysis of prognostic factors for 8-week mortality identified the following as independently adverse: age ≥80 years, complex karyotype, (≥3 abnormalities), poor performance, and elevated creatinine >1.3 mg/dl. Patients with 0, 1, 2, or ≥3 factors had estimated 8-week mortality rates of 16%, 31%, 55%, and 71%, respectively (24). Multivariate regression analysis was performed to develop risk scores for a cohort of 1406 patients (aged ≥60 years) with AML who were treated with two courses of intensive induction chemotherapy in the German Acute Myeloid Leukaemia Cooperative Group (25). They revealed that body temperature, age, *de novo* leukemia *versus* leukemia secondary to cytotoxic treatment or an antecedent hematological disease, hemoglobin, platelet count, fibrinogen, and serum concentration of lactate dehydrogenase were significantly associated with the outcome of induction chemotherapy (25). On the basis of these parameters, they designed an online risk assessment score to assist with clinical decision making (25). These reports suggest the importance of risk-adapted stratification to select the patients who should receive intensive chemotherapy that may provide better survival, rather than early death.

There are two limitations in the present study. Firstly, the number of patients evaluated was relatively small (Table I), and the evaluation was performed in a single center. The comparison among the age groups (Figure 3C) and karyotype-based sub-groups (Figure 3D) might become statistically significant with a larger number of patients. Secondly, the

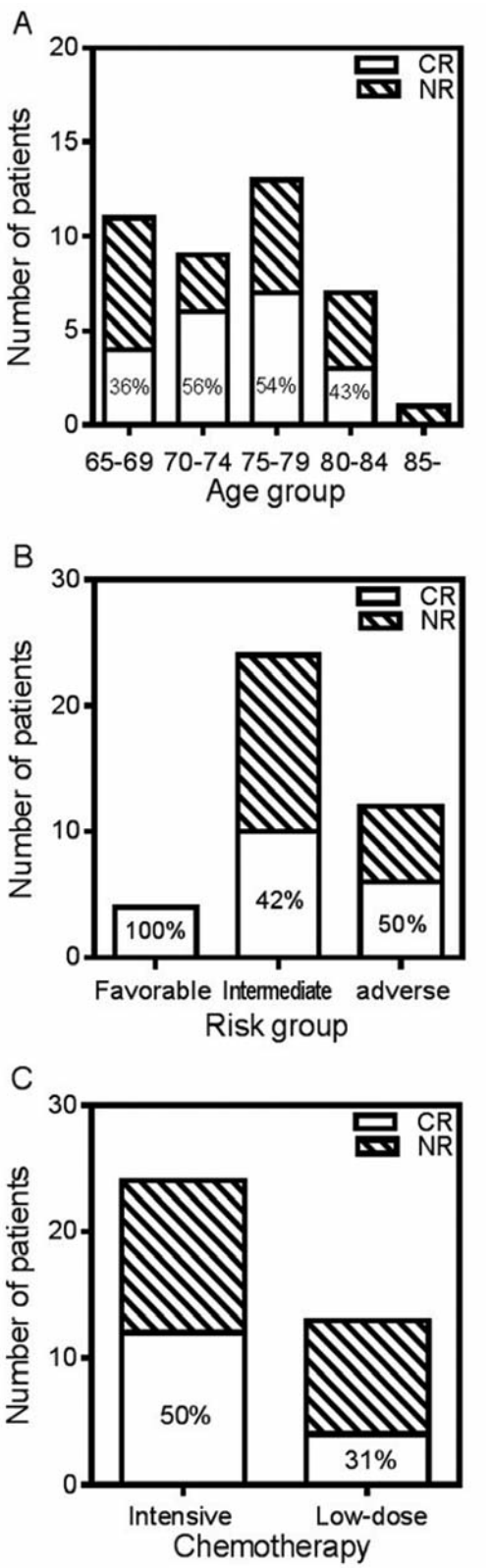

Figure 2. *The rates of patients who achieved complete remission (CR) were evaluated by the groups categorized according to age (A), karyotypic risk (B), and chemotherapeutic regimen (C).*

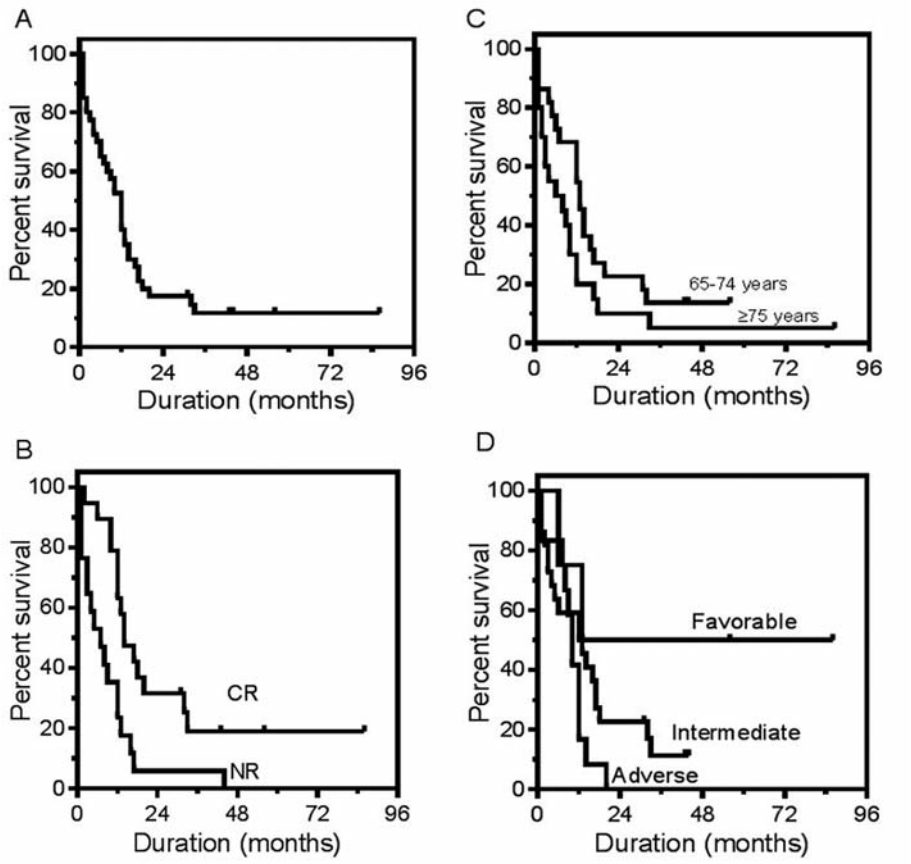

Figure 3. *Overall survival (OS) was calculated from the day of the diagnosis until death or last follow-up. Survival durations were estimated by the Kaplan--Meier method. A: The survival curve for the whole patients group. B: Survival curves according to the response to induction chemotherapy. C: Survival curves according to age. D: Survival curves according to karyotypic risk classification. The comparison was evaluated by log-rank test.*

investigation was conducted retrospectively. The treatment modality was not uniform because of the large inter-patient variability in general condition. Nevertheless, the present study conclusively suggests the necessity of achieving CR for obtaining better survival. Determination of patients who will benefit from intensive chemotherapy and the improvement of a chemotherapeutic modality along with supportive care will prolong the life expectancy of elderly patients with AML.

Disclosure Statement

The Authors have nothing to disclose concerning any of the drugs or agents considered in the present study.

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