ACUTE MYELOID LEUKEMIA IN THE ELDERLY: – 159 NAGOYA CASE STUDIES –

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ABSTRACT

To obtain background information on elderly acute myeloid leukemia (AML), unselected data covering 159 patients aged 60 years or over with AML from 14 hospitals in Nagoya, Japan was analyzed retrospectively. Among these patients, 119 had de novo acute AML, 32 had AML which evolved from myelodysplastic syndrome (MDS-AML), and 8 had other types of leukemia.

The survey showed that MDS-AML tended to be more prevalent in patients aged 70 years and older and that MDS-AML showed a significantly more severe degree of leukopenia and anemia than de novo AML. MDS-AML also showed a significantly lower complete remission (CR) rate than that of de novo AML [6.9% (2/29) vs 58.3% (67/11), $P < 0.01$] and significantly shorter survival times than those of de novo AML [median: 3.6 months vs 9.6 months, $P < 0.01$ (generalized Wilcoxon test; GW].

In de novo AML, the proportion of patients treated with conventional therapy (CT group) decreased significantly, and that of those with attenuated therapy (AT group) increased significantly as age elevated ($P < 0.01$). The CT group showed a significantly higher CR rate (65.4% vs 41.2%, $P < 0.05$) and a significantly longer survival period than those of the AT group [median: 11.6 months vs 4.8 months, $P < 0.05$ (GW)]. Overall survival rates of the older age groups became significantly shorter with aging [$P < 0.01$ (GW)].

Key Words: ELDERLY LEUKEMIA, ELDERLY AML, DE NOVO AML, AML EVOLVED FROM MDS

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INTRODUCTION

Acute leukemia is more common in older people than in young and middle-aged adults.[1,2,3] Age is one of the major adverse prognostic factors in both acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), and the prognosis is known to be poor in elderly patients.[1-5] The poor outcome of treatment is due to both host-related and intrinsic biological factors.[1] It has also been pointed out that most studies of treatment for elderly acute leukemia describe highly selected groups of patients.[4,6-8] One of the arguments for the selection bias is that some patients in each trial might be excluded by various causes, such as the eligibility criteria of a protocol or a discrete decision by the physician in charge,[6-9] and another important consideration is that the care for elderly patients with acute leukemia is often in the hands of local physician/hematologists rather than referral centers.[7] Although some elderly patients with AML have antecedent myelodysplastic syndrome (MDS-AML), it is not clear what proportion these patients represent the published series on elderly AML.[1,8] In order to obtain realistic background information on elderly leukemia regarding distribution of types, clinical features, actual treatment and outcomes, we conducted a retrospective study of 159 patients 60 years of age or older with acute leukemia admitted to 14 general hospitals in the Nagoya area between January 1990 and December 1995.

METHODS

Patients

Between January 1990 and December 1995, 159 acute leukemia patients aged 60 years or over at 14 institutes in the Nagoya area of Japan were entered in this study. Acute leukemia was defined and classified according to FAB morphological and cytological criteria[10-12] by hematologists at each institute. De novo AML was defined if no documented hematologic abnormality was identified more than 2 months before the diagnosis of AML.[13] The diagnosis of antecedent myelodysplastic syndrome was based on the FAB definition.[14]

Our analysis included clinical and biological characteristics at diagnosis such as age, sex, type of leukemia, findings of peripheral blood and bone marrow, cytogenetical analysis, WHO performance status (PS), complications, hepato-renal biochemical data, induction chemotherapy administered and its outcome and survival, as well as the attitude of the patients or physician in charge towards the treatment.

Treatments

Induction treatment was at the discretion of each hematologist in clinical charge of the patient. Treatment was classified by the physician into conventional chemotherapy (CT group), including so-called intensive or standard chemotherapy, attenuated chemotherapy (given a reduced dosage of more than 30% less than the conventional therapy: AT group) or no induction chemotherapy.

Among the 119 de novo AML cases, 4 patients, who were judged to have poor toleration of chemotherapy, were given supportive care only. Fifty-four patients (including 18 in the AT group) were treated with the induction regimen of behenoyl cytosine arabinoside (N4-behenoyl-1-β-D-arabinofuranosylcytosine; BH-AC), daunorubicin (DNR), 6-mercaptopurine (6MP), prednisolone (PSL) (BH-AC·DMP)[15] or ara-C, DNR with/without PSL. The standard dosage of BH-AC·DMP consisted of a 10- to 14- day treatment of daily BH-AC (170 mg/sqm daily 2-h i.v.), daily 6MP (70 mg/m^2 daily p.o.), and daily PSL (20 mg/m^2 daily p.o.) together with intermittent DNR (25 mg/sqm daily bolus days 1 and 2; thereafter, as necessary if a hypoplastic bone

marrow finding was not attained).[15] Nineteen patients (including one in the AT group) were treated with a combination of DNR plus cytosine arabinoside (ara-C) with/without PSL, which was administered ara-C 70–150 mg/sqm 7-day continuous infusion (c.i.) and DNR 25–40 mg/sqm bolus days 1, 2 and 3, with/without PSL (20 mg/sqm p.o. day 1–7). The number of cases with other drug combinations regimens were as follows: 9 cases in ara-C, DNR plus mitoxantrone (MIT) (1 in AT group); 7 cases in BH-AC, DNR plus VP16 with/without 6MP with/without PSL; and 26 cases including 6 cases in the AT group treated with low dose ara-C (LDAC; ara-C 10–20 mg/sqm s.c. or continuously day 14–28).

Among the 32 MDS-AML patients, BH-AC·DMP was given in 11 cases. LDAC was given to 9 patients. Other regimens were administered to 9 cases. The remaining 3 patients received no chemotherapy because of a high risk of toxic death.

All treatment was given with the consent of the patients or their guardians. Complete remission (CR) was defined by normocellular bone marrow containing normal erythroid and granular series with less than 5% blasts, accompanied by normal levels of peripheral white blood cells (WBC) and a platelet count with no circulating blasts. The duration of overall survival time was measured from either the data of the first day of induction chemotherapy or the date of diagnosis to the time of death.

Statistical Evaluation

Discrete variables were compared between groups, such as the type of disease, patient age those between 60–69 y.o. (60s), between 70–79 y.o. (70s) or between 80–89 y.o. (80s), the χ^2 test and Fisher's exact test where applicable. Continuous variables were compared between groups using Student's t-test, or were stratified into groups of comparable size and compared using the χ^2 test or Fisher's exact test. Overall survival curves were drawn by Kaplan-Meier estimates, and compared using a generalized Wilcoxon test and a log-rank test. The closing date of this study was March 31, 1996.

RESULTS

(1) Clinical and Biological Characteristics

One hundred fifty-nine cases of patients with AML aged 60 years or more were collected. Among these, 119 had de novo AML, 32 had MDS-AML, and 8 had other types; namely two cases of therapy-related leukemia, two AMLs from myelofibrosis, one AML from essential thrombocythemia, one adult T cell leukemia, one mixed leukemia, and one undetermined acute leukemia.

Table 1 compares the clinical and biological data of 119 de novo AML and 32 MDS-AML patients. The median ages were 69 y.o. for de novo AML and 72 y.o. for MDS-AML. The ratio of de novo AML/MDS-AML decreased from 5.3 (64/12) in the 60s group, 2.5 (40/16) in the 70s group, to 3.8 (15/4) in the 80s group, showing an increased tendency fowards MDS-AML incidence in patients aged 70 or more with no statistical significance (P = 0.102).

Male over female ratios were 65/54 in de novo AML and 21/11 in MDS-AML, showing male predominance in MDS-AML, but with no statistical significance.

In the FAB classification of de novo AML, the proportion of M3 decreased significantly from 17.3% (11/64) in the 60s group to 3.6% (2/55) in the 70s and 80s groups (P < 0.05).

WBC counts of MDS-AML (median: 3.250/µl) were significantly lower than those of de novo AML (median: 7600/µl, P < 0.01). The proportions of patients with WBC counts less than 4,000/µl of the total cases for a disease type group were 40.3% in de novo AML and

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56.7% in MDS-AML. The percentage of blasts in peripheral WBC was significantly less common in MDS-AML than in de novo AML (P < 0.01). Hb concentration of MDS-AML was significantly lower than that of de novo AML (P < 0.01). As for the cellularity of bone mar-

TABLE 1. Clinical and biological characteristics of elderly acute myeloid leukemia

	de novo AML	AML evolved from MDS	*P* value
Number of patients	119	32	
Age (y.o.)			
median	69	72	NS
(range)	(60–88)	(60–89)	
60–69	64	12	
70–79	40	16	
80–89	15	4	
Male/Female	65/54	21/11	NS
Peripheral blood			
WBC (/µl)			
median 7,600	7,600	3,250	P < 0.01
(range /µl)	(600–406,500)	(500–213,900)	(proportion of WBC < 4,000)
% of blast in WBC (%)			
median	47	6	P < 0.01
(range %)	(14–98)	(0–84)	
Hb (g/dl)			
median	8.3	7.3	P < 0.01
(range)	(3.5–14.4)	(4.7–10.6)	
Platelet (x10⁴/ µl)			
median	4.9	5.1	NS
(range)	(0.4–38.2)	(0.3–60.8)	
Cellularity of bone marrow			
hypoplastic	9.5%	28.0%	P < 0.05
normoplastic	25.3%	28.0%	
hyperplastic	65.3%	44.0%	
FAB morphology			
M0, M1 (L1)	23		
M2 (L2)	37		
M3	13		
M4, M5	35		
M6, M7	10		
undetermined	1		
Cytogenetics			
normal	51.9%	56.0%	
t(8, 21)	4.7%	0	
t(9, 22)	0	0	
t(15, 17)	7.5%	0	
abn. of 5 or 7	10.4%	16.0%	
other abn.	25.5%	28.0%	
Performance status			
0, 1, 2 72.0%	72.0%	80.0%	NS
3, 4 28.0%	28.0%	20.0%	
Complications necessitating treatment modification			
	13.4%	18.8%	NS

Rates of effective answers were 100% in number, age, sex, WBC and complications, 94.1% in % of blasts in WBC, 99.2% in Hb and Platelet, 84.9% in Performance Status, and 81.6% in cytogenetics.

row, hypoplastic bone marrow was less and hyperplastic marrow was more common in de novo AML than in MDS-AML (P < 0.05). However, statistical differences for these hematological parameters were not detected among the 60s, 70s or 80s subgroups of the elderly patients (data not shown). The proportion of patients with cytogenetical abnormalities was 48.1% in de novo AML and 44.0% in MDS-AML.

At diagnosis, 15.1% of all 159 patients had severe complications which influenced their treatment modality, though no statistical differences were observed among each disease type group. The complicating factors were pneumonia(6), renal failure(5), heart failure(2), sepsis(2), C-type hepatitis(2), hepatic cirrhosis(2), DIC(2), and others(3). Other items, such as WHO performance status, platelet counts, GOT, GPT, LDH, BUN and creatinine, did not show any statistically significant differences among disease types or age groups (data not shown).

(2) Induction chemotherapy

Although 115 patients with de novo AML were treated by various regimens, their remission rate was 58.3% (67/115). The CR rates in each age group were 63.5% (40/63) in the 60s, 53.8% (21/39) in the 70s and 46.2% (6/13) in the 80s, showing a somewhat decreasing tendency with aging with no statistical significance.

In de novo AML, 81 cases (68.1%) were treated with CT, 34 (28.6%) with AT and 4 (3.4%) with supportive care only. The proportions of each type of induction therapy were 87.5%, 10.9% and 1.6% in the 60s group, 52.5%, 45.0% and 2.5% in the 70s group, and 26.7%, 60.0% and 13.3% in the 80s group, thus indicating that the size of the CT group decreased significantly (P < 0.01), and conversely, that the size of the AT group increased significantly (P < 0.01) with aging.

The CR rate of the CT group was 65.4% (53/81), which was significantly higher than the 41.2% (14/34) for the AT group (P < 0.05). Although the CT group showed a significantly higher percentage of blasts in WBC (median; 62% in CT vs 38% in AT), the proportions of WBC counts less than 4,000/ml were 34.6% in CT and 50.0% in AT with no statistical significance (P = 0.122). Both CT and AT groups did not significantly differ in other hematological and laboratory findings. However, the proportion of PS 3 and 4 in the AT group was 42.9%, which was significantly higher than the 22.1% in the CT group (P < 0.05). In addition, G-CSF was given, to a significant degree, more frequently in the AT group than the CT group (59.3% vs 29.7%, P < 0.01). The frequency of complications at diagnosis was 17.6% with AT and 11.1% with CT (P = 0.324).

The attitude of patients towards treatment was evaluated by a physician and placed into one of 4 categories: positive, passive, no desire for induction chemotherapy, or unknown. The proportions, excluding 4 cases without records in de novo AML, were 59.0%, 21.3%, 0% and 19.7% in the 60s group; 35.9%, 30.8%, 5.1% and 28.2% in the 70s group; and 13.3%, 73.3%, 0% and 13.3% in the 80s group. These data indicate that a significantly higher proportion of patients less than 70 years old showed a positive attitude forwards treatment (P < 0.01), and that a significantly higher proportion of patients aged 80 or more showed a negative attitude forwards treatment (P < 0.01).

The CR rate of MDS-AML, excluding 3 cases with supportive care only, was 6.9% (2/29), which was significantly lower than that of de novo AML (P < 0.01).

(3) Survival

The median survival times were 9.6 months for de novo AML (3-year rate: 21.9%) and 3.6 months for MDS-AML (3-year rate: 8.8%).

The patients with de novo AML survived significantly longer than those with MDS-AML [P

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< 0.01 (GW), P < 0.01 (LR)].

In Fig. 1, the median survival times in de novo AML were 17.8 months for the 60s group, 7.7 months for the 70s group and 3.1 months for the 80s group. Overall survival progressively and significantly decreased with aging [P < 0.01 (GW), P < 0.01 (LR)].

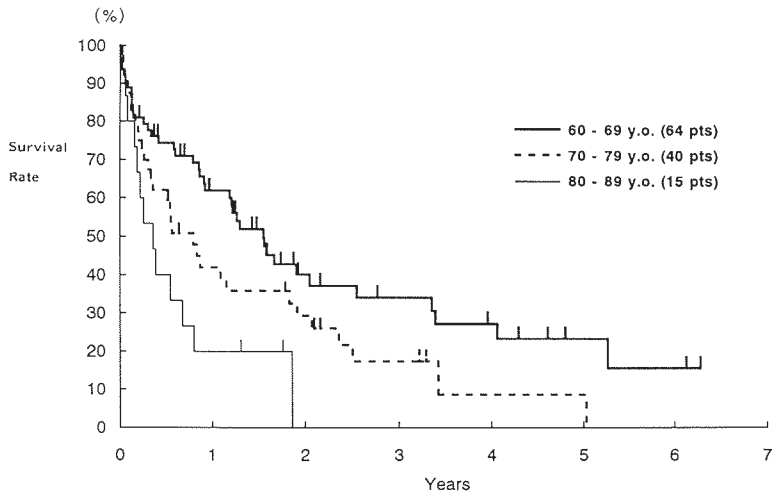Analysis of survival based on whether patients were treated with CT or AT (Fig. 2) zyielded

Fig 1. Survival time of de novo AML according to age groups.
The survival curves of patients aged between 60–69 y.o. (60s), those between 70–79 y.o.(70s) and those between 80–89 y.o.(80s) in de novo AML significantly shorten with advancing age. [P < 0.01 (generalized Wilcoxon test), P < 0.01 (log-rank test)]
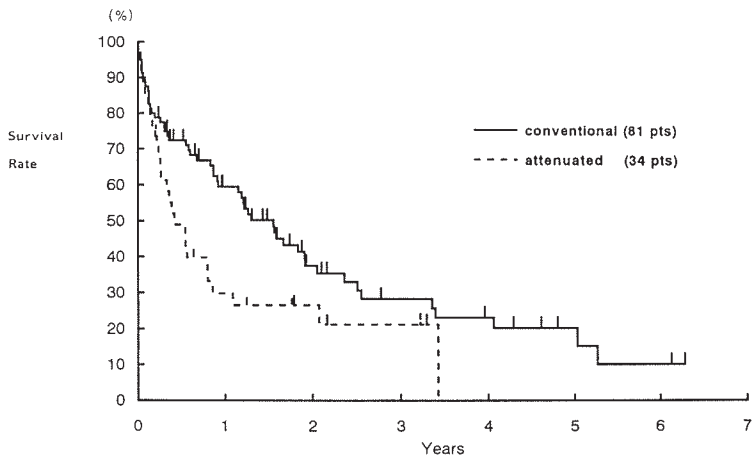

Fig 2. Survival time of de novo AML according to the intensity of induction chemotherapy.
The survival curve of the patients treated with conventional therapy (CT group) was significantly longer than that of the patients with attenuated therapy (AT group) [P < 0.05 (generalized Wilcoxon test), P < 0.05 (log-rank test)]. The median times were 11.6 months for the CT group and 4.8 months for the AT group.

a significantly longer survival curve for the CT group than that of the AT group [P < 0.05 (GW), P < 0.05 (LR)]. The median survival periods were 11.6 months for the CT group and 4.8 months for the AT group.

Early death rates within 7 days from the time of induction or diagnosis, and the death rates at 30-days were 4.2% and 11.8% in de novo AML, and 0% and 9.1% in MDS-AML, respectively.

DISCUSSION

Although a statistically significant relationship was not detected among the patient population aged 60 years or more, the incidence of MDS-AML, compared with that of de novo AML, tended to increase with age. Myelodysplasia is predominantly a disease of the elderly and approximately 30% of these cases are estimated to evolve into AML.[1] This leads to a significantly higher proportion of MDS-AML in elderly patients than in younger patients.[8] The real incidence of preleukemic myelodysplasia is difficult to ascertain in the elderly. In clinical reports the proportion of MDS-AML in elderly AML varied from 12.7% to 37.0%,[8,13,17-20] including our 21.2% (32/151) in an unselected group of AML cases. These differences have been ascribed to the background of the patient population, such as single or multi-institutional data or multi-institutional protocol studies, and to the number of patients on referrals from primary physicians. In our study, patients with MDS-AML produced a significantly lower CR rate than those with de novo AML, and survived for a significantly shorter period of time than those with de novo AML, which confirms other reports.[13,17] According to Gajewski et al.'s report, both antecedent preleukemic syndrome and advancing age were independent negative prognostic factors for achieving remission.[13] Thus, the higher incidence of MDS-AML with a poor prognosis is a fundamental feature of elderly acute leukemia.[1,5]

The proportion of the FAB M3 subtype in de novo AML became significantly lower in patients aged 70 or over than those less than 70 years of age. It was reported that the FAB M3 subtype was rare, accounting for only 1.3% and 4% of elderly patients compared with 11.7% and 16% in younger adults in a single hematological department experience[8] and population-based study,[7] respectively. This report may indicate that elderly leukemia arises from less mature leukemic clones of elderly leukemia as suggested by leukemia cytology, cytochemistry, and immunophenotype data.[1]

Although the choice of treatment for individual elderly patients was mainly left to the discretion of the physician in charge, the patient's attitude towards therapy is quite important in applying the treatment modality. In non-elderly adult AML, it is extremely rare that the patient would not desire conventional chemotherapy, which clearly has brought about the recent objective improvement in both the CR rate and the number of long-term survivals. Our data on de novo AML revealed that the proportion of patients with a "positive" attitude towards therapy decreased significantly from 59.% in patients less than 70 years old to 13.3% in those 80 y.o. and more (P < 0.01). The attitude towards chemotherapy may be influenced by such factors as chronological and physiological age, philosophy of life, socio-economic situation and understanding of the disease. The interaction between the physician and the elderly patient is also important in decision-making.[21] However, we could not investigate which factors had a more critical impact on patient preference.

In our study, the selection of a therapy for de novo AML was not carried out in a randomized fashion nor based on selection criteria. However, we found a marked trend for longer survival in elderly patients treated by conventional induction treatment. Although it could not be

determined whether this result should be attributed to the selected group of patients or to the effect of the treatment itself, this result confirms the prognostic value of therapeutic choice.[8] Many investigators now agree that intensive chemotherapy is the best choice for selected elderly patients with AML.[1] Yet, the question as to what selection criteria should be applied in the elderly remains.[1] In our comparison of CT and AT group characteristics, the criteria of age, blast percentage in WBC and PS were significant factors. Since debilitated patients with a poor PS would be candidates for the AT group, PS, which is one of the fundamental eligibility criteria in the protocol study,[8,22] would be quite an important factor in choosing appropriate therapy.[1] We did not find any laboratory data, such as albumin, RBC or BUN, to be a significant factor in selecting treatment modality. One of the interesting reports was a clinical trial for elderly patients assessed not to be able to tolerate full-scale intensive chemotherapy, which produced a 60% CR rate with a 9.9 month median survival time using oral etoposide and 6-thioguanine with idarubicin.[19] However, the eligibility criteria and the background patient population were not clearly described.

One of the main characteristics of treatments for elderly patients with acute leukemia is the high incidence of early death or therapy-related death.[1,8] The death rates varied between 0–5.0% within 7 days and between 10.0–15.0% at 30-days in the three types of acute leukemia. Induction mortality decreased from about 30% in the 1980s[23] to 10–20% in recent clinical trials.[18,20,24] One of the reasons for the reduction in our data might be because the most prevalent induction therapy used, BH-AC·DMP, was a response-oriented therapy, the drug dosages of which were adjusted depending on the hematological effects of the anti-leukemic drugs on the preceding day, signifying a 'tailor-made' regimen.[1] This suggests that careful assessment and treatment would decrease the risk of early death in elderly patients with acute leukemia.

Since it is well recognized that the chronological age of an elderly patient may differ greatly from his or her biological age, it is difficult to define a true 'elderly patient'.[1] Our data showed that patients aged 80 y.o. or more had significantly poorer survival times than those under 80 y.o. in de novo AML. The proportion of patients treated with conventional therapy and having a 'positive' outlook towards treatment were significantly low in the 80s group. Thus, we would propose that patients aged 80 or more should be handled in another category as true elderly patients.

We think that this retrospective analysis is representative of a realistic clinical spectrum of elderly acute leukemia, showing the essential background information on distribution of types and outcomes. Further study is warranted to determine what selection criteria should be applied to choose the most appropriate form of therapy in elderly patients suffering from acute leukemia.

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