HIGH INCIDENCE OF UNFAVORABLE CYTOGENETIC ABERRATIONS AND LOW REMISSION RATE IN ADULTS OVER 60 WITH ACUTE MYELOID LEUKEMIA

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Summary. Adults over 60 years of age with acute myeloid leukemia (AML) more frequently have unfavorable molecular-cytogenetic aberrations, poor response to chemotherapy and higher mortality rate than younger patients. The aim of the study was to analyze the clinical, molecular-cytogenetic and induction treatment response features of adult patients over 60 years of age with newly diagnosed AML. Seventy-seven adults (over 18 years of age) with AML were enrolled in our 3-year study. Molecular-cytogenetic aberrations, remission rates, resistant disease and early deaths were compared in the three patient groups: 18-34, 35-59 and 60 years of age or older. Our results confirmed the generally poor outcome of the older AML patients. Patients over 60 had a higher percentage (32%, $p = 0.03$) of unfavorable cytogenetic abnormalities (i.e., chromosome 5 and 7 abnormalities, t(11q23)/MLL and complex karyotypes) and a lower percentage (3.6%, $p = 0.03$) of favorable cytogenetic abnormalities (only 1 patient over 60 with t(15; 17)) than younger patients. Out of all AML cases, complete remission following initial induction chemotherapy was achieved in 41 (53.2%). The adults over 60 had the lowest complete remission rate – 35.7% ($p < 0.01$) and the highest rates of primary chemotherapy-resistant disease (28.5%, $p = 0.03$) and early deaths (53.6%, $p < 0.01$), compared to younger patients. We concluded that high frequency of unfavorable cytogenetic aberrations and adverse age were major determinants of complete remission rate in intensively treated acute myeloid leukemia patients older than 60 years. These data confirmed the need of an age-specific management for the disease in the elderly.

Key words: *acute myeloid leukemia, cytogenetics, age, treatment*

INTRODUCTION

Acute myeloid leukemia (AML) presents at all ages, but is mainly a disease of the elderly. The incidence of AML increases with age [2, 11]. In a multivariate analysis of prognostic factors, age ≥ 60 years was a statistically significant poor prognostic factor for treatment outcome. Besides the poor prognosis of adverse age, the cytogenetic findings at presentation are among the most important prognostic factors in predicting initial response to therapy, remission duration, and overall survival in AML [2, 4, 7, 10, 14, 17, 19]. Adults over 60 years with AML more frequently have unfavorable cytogenetics, poor response to chemotherapy and higher mortality rate than younger patients. Favorable-risk aberrations are relatively uncommon in the elderly, as opposed to normal and complex karyotypes [1, 2, 5, 8]. Patient-specific characteristics such as impaired physical function also influence the outcome [2, 6, 20]. Although these conclusions are generally accepted, little is known about the extent of these associations and how they vary according to the age groups.

The aim of the study was to analyze the clinical, molecular-cytogenetic and induction treatment response features of adult patients over 60 years of age with newly diagnosed, previously untreated AML.

MATERIAL AND METHODS

Model of the study

Patients: Seventy-seven adults with newly diagnosed acute myeloid leukemia were enrolled in our 3-year study. Diagnosis of AML was based on the morphologic and cytochemical criteria of the "French-American-British classification'' (FAB) [3]. First-line therapy consisted of standard-dose cytarabine combined with an anthracycline, 6-mercaptopurine or etoposide. A complete remission (CR) was defined as 5% or less blast cells in a normocellular or hypercellular bone marrow with a normal peripheral and differential blood count. Remission time (RT) was defined as time from diagnosis to remission. A resistant disease (RD) was accepted if CR was not achieved after three courses of induction therapy. Early death (ED) was death in the first three months after the beginning of induction therapy.

Methods

Conventional cytogenetics and Fluorescence in situ hybridization (FISH): Cytogenetic analyses were performed at diagnosis of AML. The bone marrow cells were cultivated by direct and indirect methods (after 48 hours of cultivation with 15% fetal bovine serum at 37°C in RPMI) to obtain metaphases. The chromosomes were stained by G-banding method and were analyzed by light microscopy and the software program Icarus Metasystem. Karyotypes were determined according to ISHC (International System for Human Cytogenetic) nomenclature [13]: clonal aberration was accepted in the presence of at least two metaphases with the same structural change or the same chromosome gain, or at least three metaphases with

deletion in the same chromosomes. FISH analysis was performed on cytogenetic preparations obtained from bone marrow cells. We used direct labeling locus specific probes (Vysis, Ltd). The part of genetically abnormal clones was determined upon analysis of at least 100 successfully hybridized cells.

Statistical analysis

Comparison of quantitative variables among patient age groups was made by one-way analysis of variance. A comparison of qualitative data was performed by means of the Chi-Square and T-test. All statistical tests were two-sided. Probability values less than 0.05 were considered statistically significant.

RESULTS AND DISCUSSION

The determination of risk factors in acute leukemia has been a target of large randomized international studies [4, 7, 9, 15]. Age-related changes in tumor biology are major determinants of poor outcome in older adults with AML [2, 9].

Patients' characteristics

Clinical, biological and laboratory features of untreated AML cases are presented in Table 1. According to age, patients were divided in 3 groups: 18-34 (21%), 35-59 (43%) and over 60 years (36%). The mean age of all studied patients was 52 years (range 18-84); 43 patients (56%) were male and 34 (44%) were female. The median white blood cell count was 24.0×10^9/l (range $0.9\text{-}319\times10^9$/l).

Table 1. Biologic and laboratory characteristics of AML adults by age groups

Parameter	18-34 years	35-59 years	60+ years	p-value
Patients, n (%)	16 (21%)	33 (43%)	28 (36%)	0.05
Age, median (range)	26.5 (20-34)	47 (35-59)	67.5 (60-84)	
Sex, male/female	10/6	17/16	16/12	0.9
Laboratory data, median (range)				
Hgb, g/l	83.5 (52-147)	79 (40-133)	81.5 (50-120)	0
WBC x 10^9/l	24.4 (1-240)	23.6 (0.9-148)	22.5 (1.1-319)	1
PLT x 10^9/l	36 (5-489)	43 (0-206)	61 (0-441)	0.02
LDH, IU/l	920 (160-6479)	927 (331-7699)	821 (266-9150)	0
Bone marrow blasts,%	70 (30-92)	62 (35-100)	58 (30-100)	0.55
Peripheral blasts, %	48.5 (15-74)	42.5 (5-89)	36 (11-94)	0.42
FAB classification, n (%)				
M0	1 (6)	6 (18)	1 (4)	< 0.01
M1	0	2 (6)	4 (14)	0.01
M2	4 (25)	7 (21)	9 (32)	0.08
M3	3 (19)	2 (6)	1 (4)	< 0.01
M4	6 (37)	7 (21)	5 (15)	< 0.01
M5	2 (13)	9 (27)	4 (14)	0.47
M6	0	0	4 (14)	0.04

Hgb indicates hemoglobin; WBC- white blood cell; PLT- platelet; LDH-lactate dehydrogenase; FAB-French-American-British

Our results showed a significant difference in the values of PLT (p = 0.02) with the highest median PLT count ($61x10^9$/l) being registered in patients over 60 years of age. AML in elderly was a less proliferative disease with lower bone marrow and peripheral blast percentages than in younger patients being studied. These lower counts may relate to AML in the elderly more often arising from an undetectable myelodysplastic syndrome as observed by some researchers [2, 9, 15]. We have also observed higher frequency of the poor prognostic FAB categories AML-M6 (14%, p = 0.04) and AML-M1 (14%, p = 0.01) in patients at 60 years or older.

Molecular-cytogenetic aberrations

Patients are divided into favorable, intermediate, and unfavorable cytogenetic groups (Table 2, Fig.1). The favorable category includes patients with inv(16), t(8; 21) and t(15; 17) abnormalities. The intermediate category includes patients with normal karyotype, trisomy 8 and few other single-chromosome deletions. The unfavorable category includes patients with complex (3 or more) aberrations, aberrations or losses of chromosomes 5 or 7, inv(3q), t(6; 9), 11q23 aberrations and t(9; 22). Six patients with uncommon cytogenetic abnormalities could not be classified in neither of the cytogenetic risk categories. The frequencies of the major specific cytogenetic abnormalities according to age are shown in Table 2.

Table 2. Molecular-cytogenetic aberrations in AML adults

Parameter	**18-34 years**	**35-59 years**	**60+ years**	**p-value**
Patients, n	16	33	28	0.05
Cytogenetic risk group, n (%)				
Favorable	5 (31.2)	2 (6.1)	1 (3.6)	0.03
Intermediate	7 (43.8)	21 (63.6)	16 (57.1)	0.7
Unfavorable	3 (18.7)	7 (21.2)	9 (32.0)	0.03
Unknown	1 (6.3)	3 (9.1)	2 (7.1)	0.93
Specific chromosomal abnormalities, n (%)				
Normal karyotype	7 (43.7)	15 (45.5)	13 (46.5)	0.99
-5/ 5q-	0	0	1 (3.6)	0.4
-7/7q-	2 (12.5)	3 (9.0)	4 (14.3)	0.13
t(8;21)/ AML1-ETO	2 (12.5)	2 (6.1)	0	0.23
inv (16)/CBFβ-MYH11	1 (6.3)	3 (9.1)	0	0.3
t(15;17)/PML-RARa	2 (12.5)	0	1 (3.6)	0.14
Trizomy 8	1 (6.3)	3 (9.1)	0	0.3
t (11q23)/MLL	0	2(6.0)	3 (10.7)	0.04
Complex karyotype	0	1 (3.0)	2 (7.1)	0.02

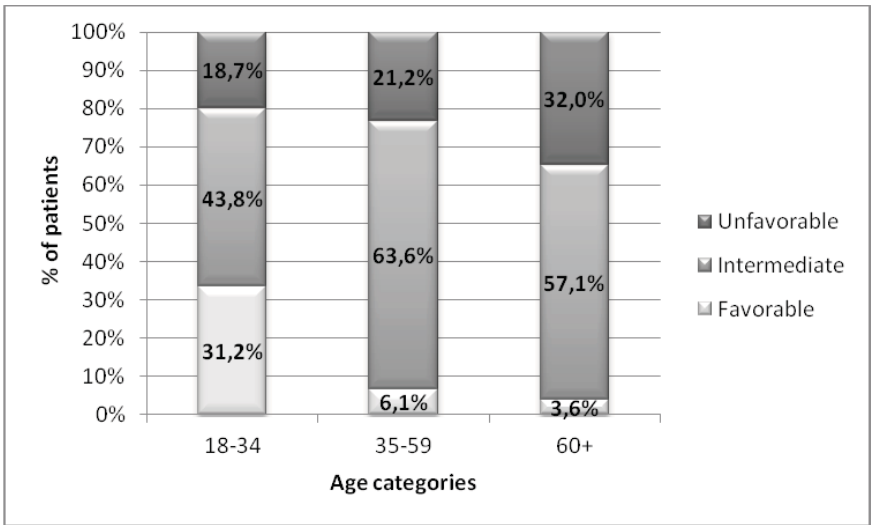

Fig. 1. Percentage of patients in the major cytogenetic risk groups by age categories

According to recent publications, cytogenetic abnormalities are identified in 50-60% of adult patients with newly diagnosed acute myeloid leukemia (AML) [12, 15, 18, 19]. We found aberrant karyotypes in 42 of all 77 (54.5%) cases. The proportion of patients with unfavorable cytogenetics (i.e., chromosome 5 and 7 abnormalities, t(11q23)/MLL and complex karyotypes) increased markedly with rising age – from 18,7% in age group 18-34 years to 21.2% and 32% (p = 0.03) in age groups 35-59 and over 60 years, respectively. Correspondingly, patients over 60 had a lower percentage (3.6%, p = 0.03) of favorable cytogenetic abnormalities (only 1 patients over 60 with t (15; 17)) than younger patients. Much of the increase in unfavorable cytogenetics was due to a marked increase in the proportions of patients with translocations, involving t(11q23)/MLL – (10.7% vs. 6% in younger patients) and deletions of whole (-7) or long arm (-7q) of chromosome 7 (14.3% vs. 9% in younger patients). AML with normal karyotypes increased with rising age and in patients aged 60 years or older the incidence was 46.5% (vs. 43.7% in the youngest age group). We found exponential increase in the incidence of AML with complex aberrant karyotypes with age – 0%, 3% and 7.1% (p = 0.02), in the three age groups, respectively. Similarly, other clinical trials report an increase of complex aberrant karyotypes as well as abnormalities of chromosome 7 in older patients and a relative rarity of favorable cytogenetic changes in older patients with AML [2, 4, 5, 7].

Treatment results

Out of all 77 patients, 41 (53.2%) achieved CR following initial induction chemotherapy – 62.5% in 18-34 age group, 63.6% in 35-59 age group and 35.7% in the group over 60 (Table 3 and Fig. 2). Nineteen (24.7%) AML patients had a primary chemotherapy-resistant disease and 27 (35%) died during the induction.

Remission rate in AML is age-dependent, with significantly lower remission rates in older adults [7, 9, 16, 19]. A similar tendency was observed in our study – the adults over 60 years of age were less likely to achieve a complete remission and the CR rates were 62.5%, 63.6%, and 35.7% ($p < 0.01$) in the age groups 18-34, 35-59, and over 60, respectively. Statistically significant differences were not revealed concerning remission time in different age groups (Table 3), but patients over 60 were with highest rates of primary chemotherapy-resistant disease (28.5%, $p = 0.03$) and early death (53.6%, $p < 0.01$).

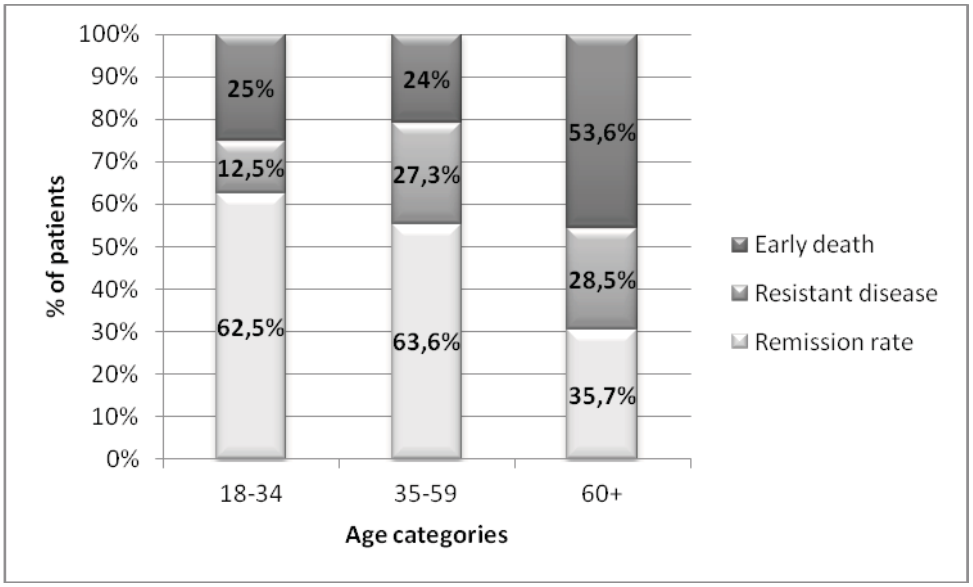

Fig. 2. Initial induction chemotherapy results by age categories

Table 3. Treatment results in different age AML groups

Parameter	18-34 years	35-59 years	60+ years	p-value
Patients, n	16	33	28	0.05
Remission rate, n (%)	10 (62.5)	21 (63.6)	10 (35.7)	< 0.01
Remission time, median months	2.6	2.0	2.13	0.95
Resistant disease, n, (%)	2 (12.5)	9 (27.3)	8 (28.5)	0.03
Early death, n (%)	4 (25.0)	8 (24.0)	15 (53.6)	< 0.01

CONCLUSION

Our results confirm the generally poor outcome of the older AML patients. High frequency of unfavorable cytogenetic aberrations and age might be major determinants for the achievement of complete remission in intensively treated acute myeloid leukemia patients older than 60 years. These data confirmed the need of age-specific management for the disease in the elderly.

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