Significance of molecular-cytogenetic aberrations for the achievement of first remission in de novo acute myeloid leukemia

Doğuştan olmayan akut miyeloid lösemiye yönelik ilk gerilemenin kazanılmasında moleküler sitogenetik aberasyonların önemi

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Abstract

Objective: The majority of adults diagnosed with acute myeloid leukemia (AML) display acquired cytogenetic aberrations at presentation. In this article, we present the major cytogenetic findings regarding AML and review their clinical significance for achievement of the first complete remission.
Material and Methods: We studied 71 adult patients with de novo AML, without previous myelodysplasia or alkylating therapy. Conventional cytogenetics and FISH were performed on bone marrow cells. The patients with AML were assigned to 12 subgroups according to established data for cytogenetic, molecular and general laboratory results. The selection of the analyzed parameters is consistent with internationally accepted "prognostic factors" in adult AML.
Results: Complete remission upon induction therapy was achieved in 40% of cases (in a mean period of 2.3 months from therapy initiation). The patients with t(15;17) PML-RARA and inv(16)/CBFbeta-MYH11ë demonstrated the highest frequency of complete remission. Patients with hypodiploidy, t(9;22)/bcr-abl and complex karyotypes were therapy-resistant or died within the first three months after AML diagnosis.
Conclusion: Molecular-cytogenetic findings have an important significance for achievement of first complete remission. However, laboratory and biologic features (age, WBC and LDH) and type of AML have a large influence on the disease outcome. *(Turk J Hematol 2008; 25: 190-4)*
Key words: Cytogenetics, FISH, acute adult leukemia, molecular analysis.

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Özet

Amaç: Akut miyeloid lösemi (AML) teşhisi konulan yetişkinlerin büyük çoğunluğu edinsel sitogenetik aberasyona sahiptir. Bu makalede AML'ye ilişkin majör sitogenetik bulgular sunulmakta ve ilk tam remisyon üzerindeki klinik anlamları incelenmektedir.

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Yöntem ve Gereçler: Miyelodisplazi tanısı konulan ve akilleyici ilaçlarla tedavi edilen de novo AML li 71 hasta incelenmiştir. Konvensiyonel sitogenetik ve FISH yöntemleri ile kemik iliği hücreleri incelenmiştir. AML hastaları sitogenetik, moleküler ve genel laboratuar sonuçlarına göre 12 alt gruba ayrılmıştır. Analiz edilecek parametreler, uluslar arası olarak kabul gören yetişkin AML hastalarında "prognostik faktörler" ile uygun olarak seçilmiştir.
Bulgular: İndüksiyon tedavisinden sonra vakaların %40'ında tam remisyon görülmüştür (tedavinin başlamasından itibaren ortalama 2.3 ay). Translokasyon (15;17) PML-RARA ve inv(16)/CBFbeta-MYH11Ñ olan hastaklarda en yüksek renmisyopn elde edildi. Hipodiploidi, t(9;22)/bcr-abl ve komplex karyotip hastalarının bir kısmı tedaviye dirençliydi kalan kısmı da AML teşhisinden sonraki ilk 3 ay içerisinde kaybedildi.
Sonuç: Moleküler-sitogenetik bulgular ilk tam remisyonun elde edilmesinde anlamlı derecede önem taşımaktadır. Ancak laboratuar özellikleri ile biyolojik özellikler (yaş, lökosit ve LDH) ve AML tipinin hastalık outcome üzerinde büyük etkisi vardır.
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Anahtar kelimeler: Sitogenetik, FISH, akut yetişkin lösemi, moleküler analiz

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Introduction

Acute myeloid leukemia (AML) is characterized with biologic, phenotypic and genotypic heterogeneity [1-4]. With the development of cytogenetic and molecular methods, it has become possible to reveal some genetic mechanisms of the leukemic process. Cytogenetics is considered one of the most valuable prognostic determinants in AML. Depending on the type of acquired genetic disturbances in leukemic cells, patients could be classified into risk groups with different therapeutic strategy. The ascribing of patients to risk groups, however, largely depends on biologic, laboratory and phenotypic features of the disease [2,5].

The determination of risk factors in acute leukemia has been a target of large randomized international studies [2,4-7,8]. Accordingly, poor prognostic markers in adult AML were determined as advanced age (over 55 years), high WBC count (over 30.10^9/L), French-American-British (FAB) M0, M1, M5, M6 and M7, and cytogenetic aberrations (-5, -7, 5q-, 7q-, 11q23, 3q and complex karyotypes). AML with t(8;21), t(15;17) or inv(16) is associated with a relatively favorable outcome. AML patients who fail to achieve complete remission (CR) after a first-line chemotherapy have a very poor prognosis and it is generally accepted that few cures are achieved at this stage [9].

The aim of our study was to search for correlations between molecular-cytogenetic aberrations in newly diagnosed AML patients and the frequency of first CR achieved upon treatment.

Materials and Methods

Patients

We studied 71 adult (over 18 years old) patients with de novo AML, without previous myelodysplasia or therapy with alkylating drugs. First-line therapy consisted of standard-dose cytarabine combined with an anthracycline ± 6-mercaptopurine or etoposide. A CR was defined as 5% or less blast cells in a normocellular or hypercellular bone marrow with a normal peripheral and differential blood count. A resistant disease (RD) was accepted if CR was not achieved after three courses of induction therapy.

Conventional Cytogenetics

Cytogenetic testing was performed at diagnosis of AML. The bone marrow was treated by direct (without cultivation) 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 [10]: 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.

Fluorescence in situ Hybridization (FISH)

FISH analyses were performed on cytogenetic preparations obtained from bone marrow cells of leukemia cases. We used direct labeling locus-specific probes (Vysis) for MLL gene rearrangements, bcr/abl fusion, PML/RARalpha fusion, inv (16)/CBFbeta-MYH11 fusion, and centromere probe cep7/7q-.

Results

The patients with AML were assigned to 12 subgroups (Table 1) according to established data for cytogenetic, molecular and general laboratory results. The selection of analyzed parameters is consistent with internationally accepted "prognostic factors" in adult AML. Hb value and PLT counts at registration were added.

Aneuploidy cases were examined separately (as group N 9 and N 10) because of their specificity. They were not included in the groups with hyperdiploidy and hypodiploidy.

In the group of "other" molecular-cytogenetic aberrations, we included patients with aberrations nonspecific for AML, with unknown prognostic significance.

We found genetic anomalies in 43 (61%) AML patients and a normal karyotype in the remaining 28 (39%) by means of conventional cytogenetics and FISH analysis.

Complete remission (CR) upon induction therapy (Table 2) was achieved in 28 (40%) of the AML patients, in a mean period of 2.3 months from therapy initiation. The patients with t(15;17)/PML-RARA and inv(16)/CBFbeta-MYH11C showed the highest frequency of CR. The patients with hypodiploidy, t(9;22)/bcr-abl and complex karyotypes were therapy- resistant or died within the first three months after AML diagnosis.

According to FAB criteria, most of the AML patients were classified as AML-M2 (25%), followed by M4 (23.9%), M5 (19.7%), M0 (9.5%), M3 and M1 (8.4%), and M6 (5.6%).

The highest frequency of CR (Table 3) was observed in AML-M3 patients (83.3%). Remission was achieved in more than 50% of AML-M2 patients (52.6%), but in those with t(8;21)-in 100% of cases. The patients with AML-M6 and AML-M0 showed the lowest frequency of CR-at 0% and 28.6%, respectively.

Discussion

There were significantly more AML patients with a normal karyotype, compared to the other molecular-cytogenetic groups. Specific features of this karyotypic group were the high mean WBC count (48.8x10^9/L) and low PLT count as compared to the group with 11q23/MLL and higher LDH as compared to t(8;21) cases. We achieved CR in 11 of 28 cases (39.3%) in a mean period of 2.3 months. Therefore, in patients with a normal karyotype, high WBC, low PLT and high LDH value could be considered as poor prognostic markers. In contrast, the presence of complex cytogenetic changes, including 5/del(5q), 3q abnormalities or 7, was found to predict a significantly poorer outcome than in patients with normal cytogenetics.

In our study, we established a double hyperdiploidy frequency, tetraploidy in particular, in comparison with hypodiploidy. In the hyperdiploidy cases, higher WBC (34.67x10^9/L vs. 17.0x10^9/L) and smaller Hb concentration alterations (90 g/L vs. 52 g/L) were observed, compared to in hypodiploidy.

According to the data from other authors [11,12], prognostic significance of hyperdiploidy and hypodiploidy in AML is unfavorable. There were higher percentages of achieved CR (50%) and lower drug resistance (50%) in hyperdiploidy as compared to hypodiploidy patients. Hypodiploidy was associated with structural changes and multiple chromosomal aberrations in 100% of cases, as well as with higher diversions of laboratory parameters.

Translocation (8; 21) was correlated with patient age mainly affecting young men (mean age 35.5 years). This aberration was uniformly distributed between FAB AML-M2 and M4. The presence of this translocation in AML-M4 is usually a rare event [13,14].

In comparison with AML patients having a normal karyotype, the frequency of CR in the t(8;21) subgroup was higher (75%) (39.3% in subgroup 1), achieved in a mean period of two months. Drug resistance was reported in one patient only (25%). These data confirm translocation t(8;21) as a favorable prognostic factor in adult AML.

One of the molecular-cytogenetic markers associated with a favorable prognosis in AML-M3 is t(15;17) [14-16]. We found t(15;17)/PML-RARA in 4.11% of AML cases. A tendency was established for relating this translocation with young patient age

Table 1. Baseline characteristics of AML patients according to molecular-cytogenetic findings

Groups	Karyotype	Number of patients	Age*	WBC*(x 10^9/L)	Hb*(g/L)	PLT*(x 10^9/L)	LDH* (UI/L)
1	Normal karyotype	28	54.32 (25-79)	48.8 (0.9-240)	82.8 (40-147)	57.5 (0-171)	1888 (348-6479)
2	Hyperdiploidy	6	56.33 (44-72)	34.67 (0.8-105)	90 (55-125)	67.2 (80-110)	781.5 (347-1929)
3	Hypodiploidy	3	57.0 (49-62)	17.0 (9.4-26.1)	52 (30-60)	62 (30-112)	1183 (378-1994)
4	t(8;21)	4	35.50 (27-49)	18.63 (9.4-24.8)	63.8 (52-97)	19.5 (15-30)	891 (283-1994)
5	t(15;17)/ PML-RARA	3	37 (22-62)	7.4 (3.1-16.0)	130 (120-147)	51 (25-78)	414
6	inv(16)/CBFbeta-MYH11	1	30	178	95	36	1271
7	t(11q23)/MLL	2	43 (39-47)	20.15 (15.1-25.2)	82.5 (43-122)	159 (112-206)	384 (378-390)
8	t(9;22)/bcr-abl	2	49.5 (44-55)	25.15 (3.0-47.3)	60 (55-64)	49.5 (80-91)	865
9	(-7/7q-)	9	48.89 (20-74)	30.0 (1.0-101.6)	80.1 (59-92)	41 (0-168)	930.2 (160-1996)
10	(+8)	7	52.71 (22-84)	35.26 (1.6-143)	93.7 (72-123)	68.8 (6-123)	2070.4 (323-7699)
11	Complex karyotype	2	61 (60-62)	20.8 (15.5-26.1)	66.5 (60-73)	57.5 (44-71)	1463.5 (1178-1749)
12	Other	4	49 (21-69)	25.3 (15.5-41.2)	82.3 (73-93)	104 (51-173)	880.3 (331-1749)

* Mean values and min-max (in parentheses)

Table 2. Frequency of achieved complete remissions in different molecular-cytogenetic AML subgroups

Groups	Karyotype	Number of patients	Patients with CR	Frequency of remissions (%)	CR (months)	Resistant patients/patients with early death (in the first 3months)
1	Normal karyotype	28	11	39.3	2.3	17 (60.7%)
2	Hyperdiploidy	6	3	50	2.7	3 (50%)
3	Hypodiploidy	3	0	0	0	3 (100%)
4	t(8;21)	4	3	75	2	1 (25%)
5	t(15;17)/ PML-RARA	3	3	100	2.3	0
6	inv(16)/CBFbeta-MYH11	1	1	100	2	0
7	t(11q23)/MLL	2	2	100	3	1 (50%)
8	t(9;22)/bcr-abl	2	0	0	0	2 (100%)
9	(-7/7q-)	9	2	22.2	2	7 (77.8%)
10	(+8)	7	3	42.8	2	4 (57.2%)
11	Complex karyotype	2	0	0	0	2 (100%)
12	Other	4	0	0	0	4 (100%)

* Mean values and min-max (in parentheses)

Table 3. Molecular-cytogenetic, biologic and laboratory data (mean values) distribution according to FAB subgroups of AML patients

	AML-M0	AML-M1	AML-M2	AML-M3	AML-M4	AML-M5	AML-M6
Number of patients	6	6	18	6	17	14	4
Normal karyotype	1	2	9	2	8	6	0
Hyperdiploidy *	1	0	3	2	3	5	0
Hypodiploidy **	2	1	2	0	3	0	3
Translocations	0	1	3	3	2	3	1
Inversions	0	0	0	0	1	0	0
Deletions	1	0	2	0	0	0	0
Complex karyotype	0	0	0	0	0	0	2
Age	46.6	66	52	39	47	52	64
WBC (x 10^9/L)	41.7	95.2	25.9	5.1	67.8	38.6	18.5
Hb (g/L)	75.4	81.3	81.1	112.5	79	87.2	70.3
PLT (x 10^9/L)	40.3	56.7	60.3	38.3	50	90.7	52.8
LDH (UI/L)	1493.6	1053	1079	380.5	1840	1625	1058
Frequency of remissions (%)	28.6	33.3	52.6	83.3	47.1	50	0

* Patients with trisomies included.

** Patients with monosomies included.

(mean 37 years). In the t(15;17)/PML-RARA group, the lowest WBC value (7.4x10^9/L) and highest mean Hb (130 g/L, $p<0.05$) were reported, compared to the other molecular-cytogenetic groups. CR was achieved in 100% of cases in a period of 2.3 months.

According to data of other authors [13,14,16-18], inv(16)/CBFβ-MYH11 is associated with a favorable prognosis and fast remission. In our case of such aberration, the period for achieving remission was not shortened, probably because of the high WBC count being a poor prognostic factor.

Cytogenetic aberrations in the chromosomal band 11q23 and rearrangement of MLL gene are important prognostic factors in AML. CR was achieved in all 11q23/MLL(+) patients in a mean period of three months. In one of the patients, CR was achieved later-in the 4th month, due to therapy resistance. Translocation 11q23/MLL in AML is associated with unfavorable prognosis. The data from our study corresponded with the publications of Abdou [19] (2002), Munoz [20] (2003), Schoch [21] (2003) for difficult remission in 11q23/MLL(+) patients.

Translocation t(9;22) and fusion gene bcr-abl were found in two (2.74%) of our AML patients-one with AML-M2 and one with AML-M5. In both cases, RD and early death occurred.

One of the more frequently found aberrations in our study of AML was monosomy 7 and/or deletion of 7q-in 9 of 71 (13%) cases with AML. Aberration -7/7q- was presented only as a single molecular-cytogenetic anomaly with a higher frequency in AML-M0, M2 and M6. According to published data [22-26] -7/7q- is a poor prognostic factor. Our results are entirely in agreement with these data, and CR was achieved in only two cases (22.2%). Drug resistance and early death were reported in the remaining 77.8% of patients.

In 86% of trisomy 8 cases, it represented a single numerical aberration and in 14%-an additional change in PML-RARA(+) AML-M3. A lot of cases with trisomy 8 were found in AML-M2 and M5. Low CR (33.3%) and high frequency of RD (66.7%) were established in the cases with (+8) as a single aberration. In the case with PML-RARA(+) karyotype, trisomy 8 probably had no influence, since lasting CR was achieved quickly.

All patients with a complex karyotype (multiple chromosomal and gene anomalies) had AML-M6 highest mean age (61 years) and high LDH value (1463.5 UI/L). Analyzing all features of this subgroup, we concluded that the complex karyotype was associated with a poor prognosis and low frequency of CR.

In conclusion, we established in this study a dependence between the frequency and type of molecular-cytogenetic aberrations and the age of AML patients. There is increased frequency of chromosomal abnormalities with poor prognostic significance (hyper- and hypodiploidy, -7/7q-, trisomy 8) and multiple chromosomal and gene anomalies with ageing.

Molecular-cytogenetic findings have an important significance for achievement of first CR, and our data are in keeping with the publications in the scientific literature [2,4-7,10]. However, laboratory and biologic features (age, WBC and LDH) and type of AML have a large influence on the disease outcome.

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