Favourable Prognostic Factors in Therapy Related Acute Myeloid Leukaemia

Nebojša Antonijević[1,2], Nada Suvajdžić[1,2], Tatjana Terzić[3], Branko Jakovljević[4], Gradimir Janković[1,2], Ivo Elezović[1], Rajko Milošević[1], Milica Čolović[1,2]

[1]Clinic of Haematology, Clinical Centre of Serbia, Belgrade, Serbia;
[2]Faculty of Medicine, University of Belgrade, Belgrade, Serbia;
[3]Institute of Pathology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia;
[4]Institute of Hygiene and Medical Ecology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

SUMMARY

Introduction Therapy related acute myeloid leukaemia (t-AML) is a distinct clinical entity recognized by the World Health Organization classification occurring after chemotherapy and/or radiation treatment administered for a previous disease. T-AML is characterised by pancytopenia, three-lineage myelodysplasia, high frequency of unfavourable cytogenetics and short survival.

Objective The aim of this study was to analyse clinical, cytogenetic, and cytological characteristics of t-AML and their impact on survival.

Methods Seventeen patients with t-AML (8 male and 9 female; median age 59 years) were identified among 730 consecutive patients with acute myeloid leukaemia. The degree of three-lineage dysplasia as well as haematological, cytological and cytogenetic analyses, were assessed by standard methods.

Results The patients survived a median of 62.5 days with the 10% probability of survival during two years. Prognostically favourable factors were a higher percentage of dysplastic granulocytic cells, age less than 60 years, and presence of prognostically favourable karyotype inv(16), t(15;17), t(8;21).

Conclusion The stated prognostic factors that include age, cytogenetics findings and granulocytic dysplasia analysis could contribute to adequate risk stratification of t-AML, though fuller results would require additional analyses.

Keywords: therapy related acute myeloid leukaemia; cytology; myelodysplasia; survival

INTRODUCTION

Therapy related acute myeloid leukaemia (t-AML) is a well-recognized clinical entity occurring as a complication after chemo and/or radiation therapy administered for a prior neoplastic or non-neoplastic disease [1-28]. t-AML accounts for 5% (2-10%) of all acute myeloid leukaemia (AML) cases. It is characterised by pancytopenia, multilineage dysplasia, high frequency of unfavourable cytogenetic findings and short survival [1, 10, 18, 21-28].

Two subsets of t-AML are generally recognized. The most common, classical t-AML occurs 5-10 years following exposure to alkylating agents and/or ionizing radiation. Patients often present with therapy related myelodysplastic syndrome (t-MDS) and unbalanced chromosomal abnormalities frequently of complex nature and involving chromosomes 5 and/or 7 [1]. The second category of t-AML encompassing 20-30% of patients has a latency period of about 1-5 years and follows the treatment with topoisomerase inhibitors (epipodophylotoxins, doxorubicin, mitoxantrone). Most patients in this subset present with overt AML, without t-MDS phase and with balanced chromosomal translocations [1].

OBJECTIVE

The aim of this study was to analyse retrospectively clinical, cytological and cytogenetic features of t-AML patients, and their impact on survival.

METHODS

Patients

This retrospective series consists of 17 patients with t-AML (eight males and nine females; median age 59 years) among 730 consecutive AML patients seen at the Clinic of Haematology, Clinical Centre of Serbia, Belgrade, over a 7-year period (Table 1).

Bone marrow sampling

Following informed consent, bone marrow (BM) cells were collected by aspiration from the sternal manubrium using a standard needle and 20 ml syringe with heparin anticoagulation. The BM aspirations underwent cytochemical and cytogenetic study.

Correspondence to:
Nebojša ANTONIJEVIĆ
Emergency Centre
Clinical Centre of Serbia
Pasterova 2, 11000 Belgrade
Serbia
drantoni@gmail.com

Morphology and cytochemistry

BM smears were stained with a May-Grünwald-Giemsa, peroxidase, Sudan black B, periodic acid-Schiff, α-naphthyl-butyrate-esterase and naphthol-AS-D-chloroacetate according to standard methods and classified according to the French–American–British (FAB) classification [6]. Two distinct observers evaluated myelodysplasia in BM smears according to the criteria by Bennett et al. [6]. Namely, at least 200 neutrophils and precursors, 200 erythroblasts and at least 30 megakaryocytes (Mk) were evaluated for dysplasia. The method by Esteinne [11] was applied for the categorization of dysplasia; dysplasia in 25-50% of erythroblasts and granulocytes/precursors were graded as moderate and as marked when ≥50% cells affected. Dysmegakaryocytopoiesis was defined as the presence of at least 50% of dysplastic megakaryocytes in BM.

Cytogenetic analysis

Chromosome preparation was carried out either directly or after a non-stimulated short-term culture of BM cells for 24-48 hours, according to HG banding methods [14, 20]. Karyotypes were designated according to the ISCN. Pre-treatment karyotype was categorized according to Grimvade [12] as follows: 1) favourable: t(15;17), inv(16)/t(l6;16), t(8;21) alone or with other changes; 2) adverse: complex karyotype (≥5 unrelated abnormalities), -5, del(5q), -7, del(7) alone or in conjunction with other intermediate risk or adverse–risk abnormalities 3) intermediate (standard): normal and other abnormalities not classified as adverse or favourable.

Statistical analysis

In addition to the standard methods of descriptive and analytical statistics (Cox's regression multifactorial analysis, Mann–Whitney U-test, Kruskal–Wallis unifactorial nonparametric variance analysis, Spearman's rank correlation, Student's t-test for independent samples), the standardized Greenwood's formula was used for the assessment of overall survival (OS) rates according to age, presence/degree of BM dysplasia and cytogenetic risk.

RESULTS

Clinical findings, treatment and bone marrow findings

Relevant clinical and cytomorphological data of 17 t-AML patients are presented in Table 1. The median time-to-t-AML between the primary diagnosis and t-AML was 72 months (range 9-336 months).

Marked (>50% dysplastic cells) and moderate (25-50% dysplastic cells) erythroid dysplasia was registered in 5/16

Table 1. Clinical findings prior treatment, bone marrow cytomorphology and survival in 17 patients with t-AML

Number of case, sex and age at t-AML onset	Prior disease	Prior treatment	Time to t-AML occurrence (months)	FAB type	Bone marrow cytology				Survival after diagnosis of t-AML (days)
					Blasts (%)	Dysplastic cells (%)			
						Erythroid lineage	Granulocytic lineage	Megakaryocytic lineage	
1/M/67	Renal cell carcinoma; urinary bladder carcinoma	Operation, radiotherapy	72	M2	82	34.4	68	ND	23
2/M/56	Essential thrombocythemia	Busulfan*	168	M2	75	ND	ND	ND	90
3/F/58	CSIIIB; Hodgkin's disease CS IIIB	MOPP*	72	M4	42	49.4	100	61.5	90
4/F/60	Multiple myeloma CS III	M-2*, ABP*	72	M6	34	31.2	75.7	8.6	30
5/M/17	Hodgkin's disease CS IIIB	MOPP*, radiotherapy	72	M4	88	70.1	87.7	Absence of Mk	365
6/F/71	Breast carcinoma	FAC	132	M1	93	41.2	100	50	210
7/F/52	Breast carcinoma	FAC	25	M4	80	57.1	53.3	Absence of Mk	45
8/M/63	Polycythemia rubra vera	Busulfan*	48	M2	38	38 ring	93.3	64.3	7
9/M/35	Aplastic anaemia	Prednisone, azathioprine	96	M4	60	90.4	80.4	Absence of Mk	10
10/F/65	Essential thrombocythemia	Busulfan*	336	M2	61	46.5	38.5	94.1	20
11/F/19	Hodgkin's disease CS IIIB	ABVD*, radiotherapy	23	M3	70	32.1	90.6	Absence of Mk	>760
12/M/59	Polycythemia rubra vera	Busulfan*	144	M2	35	57.1	98.7	100	180
13/F/71	Multiple myeloma CS II	M-2*	84	M4	60	49.9 ring	100	53.3	90
14/F/72	Aplastic anaemia	Prednisone, azathioprine	12	M2	60	23.7	14.3	50	30
15/M/63	Prostatic carcinoma	Cyproterane acetate, radiotherapy	9	M2	88	66.1	97.5	100	79
16/F/32	Limfoblastni limfom CS IA; lymphoblastic lymphoma CS IA	LALA84*,**	27	M5	78	28.0	81.98	Absence of Mk	>180
17/M/38	Non-Hodgkin's lymphoma, follicular, IIIACS	CHOP*,**	30	M4	32	33.9	34.3	75	45

* alkylating agent; ** topo inhibitor; ring – ringed sideroblasts; M – male; F – female; ND – not done; MOPP – mechlorethamine, oncovin, procarbazine, prednisone; M-2 – vincristine, carmustine, cyclophosphamide, melphalan, prednisone; ABP – adriablastine, carmustine, prednisone; FAC – 5-fluorouracil; adryamicyne, cyclophosphamide; ABVD – adriablastine, bleomycin, vinblastine, dacarbazine; LALA84 – prednisone, vincristine, cyclophosphamide, doxorubicine, methotrexate, L-asparaginase; CHOP – cyclophosphamide, doxorubicine, vincristine, prednisone

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and 10/16 analysed patients, respectively. The most prevalent dysplastic features in the erythroid lineage were karyopyknosis (15/16) and megaloblastosis (14/16). Karyorrhexis, Howell-Jolly bodies and multinuclearity were found in 12/16, 8/16 and 7/16 patients, respectively. Ringed sideroblasts were detected in two patients. PAS positive erythroblasts were observed in a single patient with AML-M6.

Marked (>50% of dysplastic nonblastic cells) and moderate (25-50% of dysplastic nonblastic cells) granulocyte dysplasia was found in 13/16 and 3/16 patients, respectively. The most prevalent dysplastic features of the granulocytic series were hypogranulation seen in all patients, pseudo Pelger-Huët anomaly (11/16), pseudo-Chediak abnormally large granules (9/16) and cytoplasmic vacuoles (4/16).

Dysplasia of the megakaryocytic (Mk) lineage (>50% dysplastic Mk) was present in 7/11 analysed patients. The most frequent dysplastic features were Mk with hypolobulated nuclei (9/11), Mk with small bead-like nuclei (8/11), micromegakaryocytes (5/11) and Mk with cleaved nuclei (2/11).

Table 2. Cytogenetic findings in 17 t-AML patients

Patient	Karyotype
1	59, XY, +1, +2, +6, +9, +10, +11, +13, +14, +15, +15, +18, +2 mar 2[9] / 46, XY [11]
2	46, XY [20]
3	46 XX, inv(16)(p13;q22) [20]
4	46, XX, der(7) [20] / 46, XX / [13]
5	Not done
6	46, XX [20]
7	46, XY [20]
8	46, XY [20]
9	47, XY, t(12;12) (p13;q13), +21 [20]
10	46, XX, del (20q)(q11) [16] / 47, XX, idem+ mar1 [4]
11	46, XX, t(15;17)(q22;q11-21) [17] / 46, XX [3]
12	45, XY, -8 [12] / 46, XY [20]
13	45, XX, -5, +12, -21, -22, +mar [2] / 45, XX, der(3), -5, +12, add 14(p10), -21, -22, +mar [12] / 43, XX, der(3), -5, +12, add 14(p10), -16, -17, +2 mar [1] / 46, XX [3]
14	Not done
15	45, X, -Y, t(8;21)(q22;q22) [3] / 46, XY [17]
16	Not done
17	46, XY, dup(4)(q22), -17, +mar [14] / 47, XY, -X, dup(4)(q22), +2 mar [6]

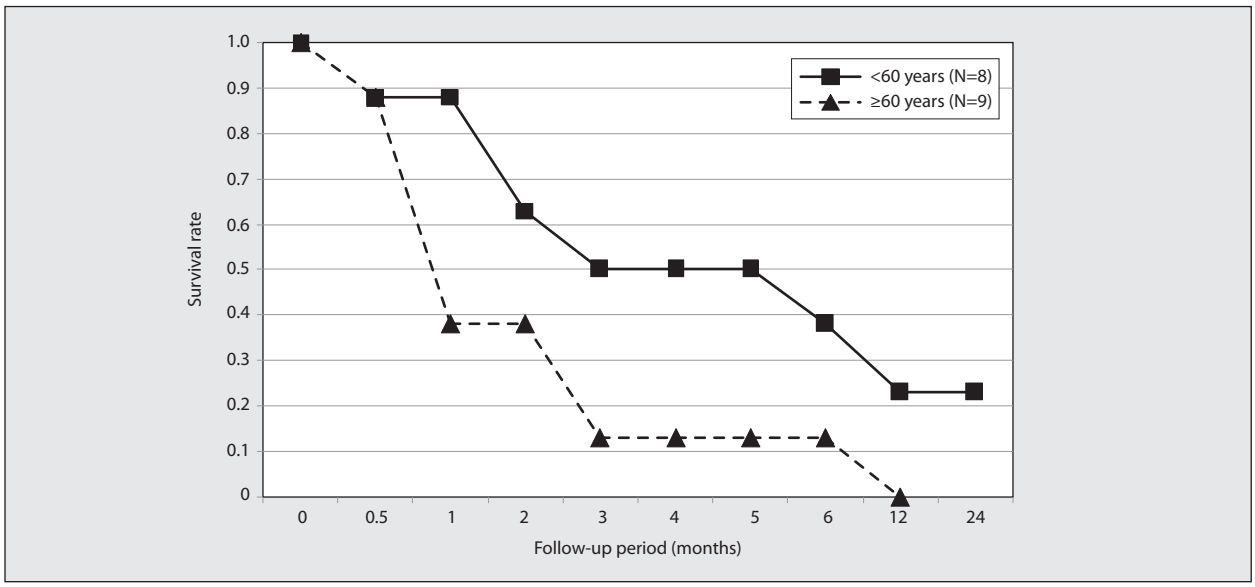
Cytogenetic analysis

Cytogenetic information was obtained for 14/17 patients, while chromosome abnormalities were registered in 10/14 evaluated patients (Table 2).

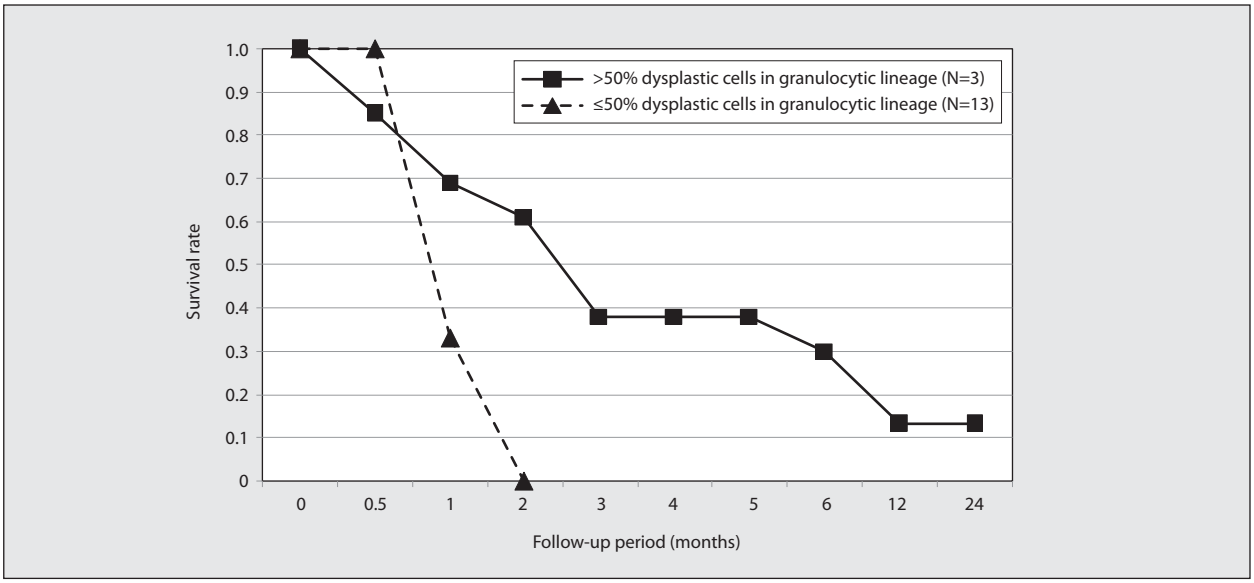
Survival

We investigated the correlation of overall survival (OS) compared to age, time-to-t-AML, organomegaly, degree of erythroid lineage, granulocyte count, Mk dysplasia and cytogenetic category. A statistically significant correlation was found between probability of survival and age (Graph 1), degree of granulocytic dysplasia (Graph 2) and favourable karyotype (Graph 3). Cox's regression multifactorial analysis showed that favourable prognostic factors were <60 years (p=0.016) and higher degree of dysplasia in granulocytic lineage (p=0.034). Greenwood analysis also added to the aforestated two factors, younger age (Z=2.412) and higher dysplasia percentage in granulocytic lineage (Z=4.561), and the presence of favourable karyotype versus unfavourable karyotype (Z=2.739). At the same time the degree of dysplasia in both erythroid and megakaryocytic lineages was without prognostic relevance for OS in t-AML in our series.

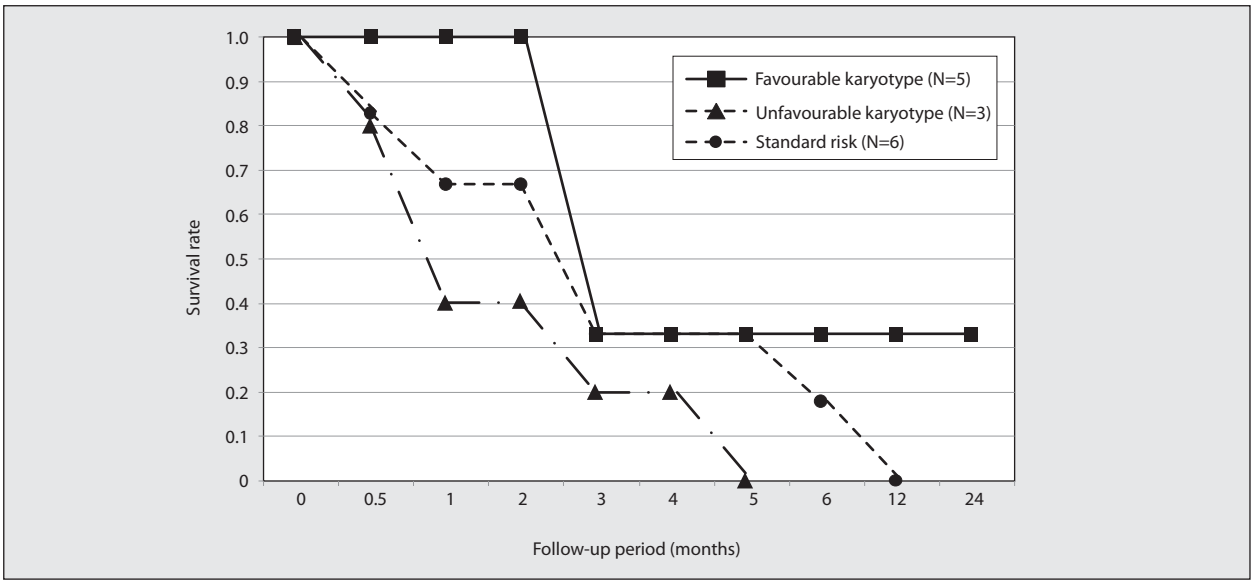
Median OS of patients ≥60 years was 25 days, and 90 days among patients <60 years (Graph 1). The probability of OS at any time point was higher among younger patients, but the statistically significant difference between the groups was observed only at the time point of 30 days (Z=2.412; p<0.05).



Graph 1. Median survival of the patients in relation to age



Graph 2. Median survival of the patients in relation to degree of granulocytic dysplasia



Graph 3. Median survival of the patients in relation to favourable karyotype

The median OS in the group with ≤50% dysplastic cells in granulocytic lineage was 25 days, compared to 45 days in patients with >50% dysplastic cells in granulocytic lineage (Z=4.561; p<0.01) (Graph 2). Whereas all patients with ≤50% dysplastic cells in granulocytic lineage died within two months, one subject with AML-M3 and >50% dysplastic cells in granulocytic lineage lived longer than 24 months (and is still alive). At the same time, dysplasia in both erythroid and megakaryocytic lineages was without prognostic relevance on OS in t-AML patients in our series.

The median OS in the patients with favourable karyotype was 90 days, compared to 23 days in patients with unfavourable karyotype (Graph 3). The probability of OS at any time point was higher among younger patients, but the statistically significant difference between the groups was observed only at the time point of 15 days to 60 days (Z=2.739; p<0.05).

DISCUSSION

The incidence of t-AML in our AML series of 2.3% in the period of 7 years was considerably lower than 13% previously reported by Haase et al. [12], but similar to 2% reported by Michels et al. [18]. The median age of our patients was 59 years, which corresponds to the Pedersen-Bjergaard's data [21]. The average time-to-t-AML was 6 years, which is in agreement with previous studies [10, 21, 24]. Our study confirmed the published data suggesting that the majority of the patients had been previously exposed to alkylating drugs: cyclophosphamide (five patients), busulfan (four patients), procarbazine (three patients) and melphalan (two patients) [8, 21, 24]. Only four patients had received topoisomerase II inhibitors (etoposide or doxorubicin) along with alkylating agents. Such a distribution of our t-AML patients

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according to the prior cytostatic is similar to previous reports [3, 23].

Besides the fact that t-AML risk is more often associated with chemotherapy according to some investigators, other state that the haematological malignancy risk is increased following radiotherapy for certain malignancies [29, 30, 31]. Radiotherapy in conjunction with chemotherapy additionally increases the risk of t-AML [32, 33]. Four of our 17 t-AML patients had been previously treated with radiotherapy, one receiving radiotherapy alone as the treatment for urinary bladder carcinoma, while the remaining three received combined radiotherapy and chemotherapy; one of them for myeloma and other two for Hodgkin's disease (Table 1).

The results of our study show that three-lineage myelodysplasia is a frequent finding in t-AML, as confirmed by others [10].

Cytogenetic abnormalities were found in the majority of patients, which corresponds to other studies [10, 22]. Favourable, adverse and intermediate karyotype was registered in three, three and eight cases, respectively. Anomalies of chromosomes 5 and 7 were found in only 2/14 patients.

Comparable to other studies, OS of t-AML patients was 4.42 months (mean survival: 1.5-7 months) [10, 22].

The probability of survival was significantly lower in patients ≥60 years compared to patients <60 years. This is in accordance with the findings of other studies analysing the prognostic criteria in t-AML [10, 22].

The presence of dysplasia of more than one cell lineage is considered a poor prognostic factor in t-AML, correlating with poor response to therapy, shorter remission duration and shorter OS [19, 22, 23]. In contrast, we revealed a statistically longer OS in the patients with granulocytic dysplasia, especially that of marked degree. This is probably the result of younger ages of the patients with pronounced dysplasia, as well as of the small sample. Our result resembles the data by Estienne who reported that AML, but not t-AML patients with favourable karyotype generally had dysplasia of granulocytic lineage [11]. All the three patients with favourable karyotype from our series had marked granulocytic dysplasia, which is in agreement with Estienne's report. The degree of erythroid and Mk dysplasia, in our study, as well as in other studies, failed to show impact on OS [9, 11].

Furthermore, patients with favourable karyotype had a significantly longer OS compared to unfavourable karyotype, which is in agreement with other authors' findings [16, 20, 26, 28]. Likewise, the shortest 25-day median OS was registered in patients with unfavourable karyotype compared with median survival of 80 days in patients with favourable karyotype. This result parallels those in the literature [20, 26].

CONCLUSION

It must be taken into account that t-AML is regarded as an entity of poor prognosis and is to be treated as high-risk AML. However, due to the progress in elucidating the impact of cytogenetic and molecular markers for the prognosis and treatment outcome, the entity of t-AML may be as heterogeneous as de novo AML. Thus, a scoring system encompassing at least age, cytogenetics and granulocytic dysplasia is needed to subdivide this entity.

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Повољни прогностички фактори код болесника с акутном мијелоидном леукемијом изазваном претходним лечењем

Небојша Антонијевић[1,2], Нада Сувајџић[1,2], Татјана Терзић[3], Бранко Јаковљевић[4], Градимир Јанковић[1,2], Иво Елезовић[1], Рајко Милошевић[1], Милица Чоловић[1,2]

[1]Клиника за хематологију, Клинички центар Србије, Београд, Србија;
[2]Медицински факултет, Универзитет у Београду, Београд, Србија;
[3]Институт за патологију, Медицински факултет, Универзитет у Београду, Београд, Србија;
[4]Институт за хигијену и медицинску екологију, Медицински факултет, Универзитет у Београду, Београд, Србија

КРАТАК САДРЖАЈ

Увод Акутна мијелоидна леукемија изазвана претходним лечењем (енгл. *therapy-related acute myeloid leukaemia – t-AML*) посебан је клинички ентитет у класификацији Светске здравствене организације. Она се јавља након примене хемиотерапије, односно зрачне терапије претходне болести. Одликују је: панцитопенија, линијска дисплазија, висока учесталост цитогенетских аномалија и кратко преживљавање.

Циљ рада Циљ студије је био да се анализирају клиничка, цитогенетска и цитолошка обележја *t-AML* и њихов утицај на преживљавање болесника.

Методе рада Међу 730 болесника с акутном мијелоидном леукемијом код 17 је дијагностикована *t-AML* (осам мушкараца и девет жена; просечна старост болесника била је 59 година). Степен трилинијске дисплазије одређиван је, уз цитолошке, хематолошке и цитогенетске анализе, стандардним поступцима.

Резултати Болесници су у просеку преживљавали 62,5 дана, а вероватноћа преживљавања у току две године била је 10%. На преживљавање су позитивно утицали следећи фактори: висок степен дисплазије у гранулоцитној лози, старост до 60 година и прогностички повољан кариотип – *inv(16), t(15;17), t(8;21)*.

Закључак Наведени прогностички фактори, који обухватају старосно доба, цитогенетске налазе и анализу гранулоцитне дисплазије, могли би допринети одговарајућој стратификацији ризика код болесника са *t-AML*, али су за потпуније резултате потребна додатна испитивања.

Кључне речи: леукемије изазване лечењем; цитологија; мијелодисплазија; преживљавање

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