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Biological features and outcome of biphenotypic acute leukemia: a case series

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BACKGROUND: Biphenotypic acute leukemia (BAL) is a distinct entity that is immunophenotypically defined by the European Group for the Immunological Classification of Leukemia (EGIL) scoring system and accounts for less than 5% of all acute leukemia cases. Since it is a rare and heterogeneous form of acute leukemia with an allegedly poor outcome, there is no consensus on the best treatment approach in these patients. Our objective was to analyze the biological features and outcome of patients diagnosed with BAL in our institution.

PATIENTS AND METHODS: Using the EGIL system, we identified 21 cases (3.9%) of BAL from 535 newly diagnosed acute leukemia patients in an 11-year period.

RESULTS: There were ten cases of myeloid+B-lymphoid leukemia, eight cases of myeloid+T-lymphoid, one case of B+T-lymphoid and two cases of trilineage (myeloid+B+T-lymphoid leukemia). The complete remission (CR) rate with high-dose chemotherapy was 72% and overall survival at 5 years was 21%. Patients that received acute lymphoblastic leukemia-oriented chemotherapy had a higher CR rate compared with those who received acute myeloid leukemia-oriented chemotherapy (100% vs. 60%, *P*=.007). The white blood cell count at diagnosis was found to have statistically significant impact on survival.

CONCLUSION: Despite the progress in the treatment of acute leukemia, the prognosis of BAL remains poor and treatment protocols devised explicitly for this entity should be investigated in prospective collaborative studies.

After the European Group for the Immunological Classification of Leukemia (EGIL) first published its definition of biphenotypic acute leukemia (BAL) in 1995,[1] BAL was recognized as a distinct entity by the 2001 World Health Organization (WHO) classification of hematopoietic tumors.[2] Whereas co-expression of markers of different lineages in acute leukemia (AL) is quite common (the incidence of acute myeloid leukemia (AML) co-expressing lymphoid markers and acute lymphoblastic leukemia (ALL) co-expressing myeloid markers ranges from 5% to 50% and 10% to 30%, respectively),[3] BAL is diagnosed infrequently and accounts for 4% to 5% of all cases of AL.[2] The EGIL definition is immunophenotype based and takes into account the number and the degree of specificity of myeloid or lymphoid antigens expressed by leukemia blasts.[1,2] Consequently, four patterns of co-expression can be identified: myeloid + B-lymphoid, myeloid + T-lymphoid, trinlineage (myeloid + B+T- lymphoid) and B+T-lymphoid, out of which the latter two are found extremely rarely. The cell of origin is assumed to be the multipotent progenitor-cell with the capability of differentiating along both myeloid and lymphoid lineages.[2] Subsequently, according to the FAB classification, BAL blasts can resemble lymphoblasts (L1 or L2 morphology) or can be classified as AML on the basis of standard morphology and cytochemistry (M1, M2, M4, M5 subtypes).[4] On cytogenetic analysis, there is a high incidence of the Philadelphia (Ph) chromosome, rearrangements involving 11q23 and complex abnormalities,[5,6] but so far no distinct karyotypic abnormality has been reported of being associated exclusively with BAL except trisomy 4 which is mostly associated with BAL.[7] BAL affects both adults and children, and although more than ten years have elapsed since the EGIL publication on its definition, there is still no consensus on the most appropriate treatment of these patients. The choice of chemotherapy is either morphology-based, or frequently treatment schemes for ALL are used.[8,9] There have also been attempts on the use of combined

treatment schemes.[10] So far, the treatment outcome of BAL has been considered to be poor, but lately a number of different reports has been published.[5,9,11]

The aim of this study was to review the clinical data with relation to the outcome in the cohort of BAL patients treated in our center.

PATIENTS AND METHODS

We reviewed the clinical and laboratory data for adult patients treated for newly diagnosed acute leukemia at the Zagreb Clinical Hospital Center (Croatia) between December 1995 and December 2006. Out of 535 AL patients, 21 patients (3.9%) were classified as BAL according to the EGIL criteria.

The AL diagnosis was established using the FAB criteria and revised according to the WHO classification. The immunophenotype was assessed with a standard procedure according to EGIL.[1] Cytogenetic analysis (G-banding) was successful in 15 patients and FISH analysis using Abbott Vysis LSI Bcr/abl and MLL, 11q23 probes was performed in 5 and 11 patients, respectively.

Following lysis of red blood cells, bone marrow white blood cells were immunophenotyped by using a panel of monoclonal antibodies (Mo.Abs.) and flow cytometry (FACScan and FACSCalibur, BD Biosciences, USA). The following Mo.Abs. conjugated with FITC, (R)PE, RP-CY5, PerCP and APC were used in double, triple and recently quadruple staining procedures: CD1a, CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD11b, CD13, CD14, CD15, CD16, CD19, CD20, CD22, CD33, CD34, CD41, CD45, CD56, CD64, CD65w, CD71, CD79a, c-kit/CD117, anti-glycophorin A, anti-MPO, anti-Tdt, anti-lyzozyme and anti-HLA DR. MoAbs were purchased from the three major sources: DAKO, Denmark, BD Biosciences, USA and Caltag, USA. The myeloid or B/T lymphoid markers were considered to be positive if they were expressed in >20% of blasts; myeloperoxidase was considered positive if expression was found in >10% of blasts.

Treatment

The patients who met the inclusion criteria were treated with intensive chemotherapy+stem cell transplantation (SCT) according to the European Organisation for Research and Treatment of Cancer (EORTC) protocols for the treatment of acute leukemias. Patients were classified according to cytomorphology as AML or ALL and received induction therapy and postremission therapy according to EORTC (AML10-four patients, AML12-four patients and ALL4-ten patients).[12-14] The three patients with advanced age and Karnofsky score <70% received low-dose chemotherapy. All the patients were assigned to allogeneic or autologous SCT, according to the availability of an HLA-identical related donor. Consequently, seven patients received autologous SCT in first remission, one patient received matched unrelated donor (MUD) SCT in second remission and none of the patients received a sibling allograft. All of the protocols were in accordance with the 1975 Helsinki Declaration and approved by the ethical committee of our institution according to the national legislation. Informed consent was obtained from all patients.

Outcome analysis

Outcome was assessed for patients that received intensive chemotherapy. The disease-free survival (DFS) was calculated from the date of complete remission (CR) until the date of first relapse or death in first CR. The duration of survival was calculated from the date of diagnosis until the date of death. The follow-up was assessed from the date of the diagnosis to the date of the last check-up. We tested the impact of the following parameters on CR achievement and/or survival: age (< or > median value), WBC count (< or > median value), FAB (ALL vs. AML) and BAL (myeloid+B-lymphoid vs. myeloid+T-lymphoid), subtype AML-oriented vs. ALL-oriented chemotherapy, autologous SCT vs. chemotherapy. Single factors were investigated for their impact on CR rate by the Fisher's exact test. Survival curves were calculated according to the Kaplan-Meier technique and two-tailed log-rank test was used to test the difference between the survival curves. A P value <.05 was considered statistically significant. For statistical analysis SPSS 15 software was used (SPSS Inc., USA).

RESULTS

The patient and disease characteristics, treatment and outcome are listed in Tables 1 and 2 and summarized in Table 3.The median age of the patients at diagnosis was 44 years (range, 16-74) with a male to female ratio 3:1. The median white blood cell (WBC) count, hemoglobin concentration and platelet count were 14.2×10^9/L (range, 0.9-296), 101 g/L (range, 47-149) and 49.5×10^9/L (range, 7-285), respectively. Morphological assessment showed myeloid features in nine, lymphoid features in six and undifferentiated in six patients. G-banding was successful in 15 patients. Normal cytogenetic findings were present in four patients, numeric changes in five patients and structural changes in five patients, while one patient had a complex karyotype; Philadelphia chromosome was identified in 4/20 patients. Abnormalities involving the MLL

Table 1. Patient characteristics and biphenotypic acute leukemia diagnosis.

Pateint No.	Sex, Age (y)	WBC ($\times 10^9$/L)	BM blasts (%)	FAB	Antigens positive	EGIL scores[a]			Cytogenetics /FISH/
						My	B	T	
1	M, 69	16.2	87	UD	CD79a+CD19+CD20+TdT+MPO+CD13+CD15+	**3.5**	**4.5**	0.5	53-54,xy
2	M, 25	5.3	88	L2	cCD22+CD19+TdT+MPO+CD33+	**3**	**3.5**	0.5	46,xy
3	F, 36	6.9	54	M2	CD79a+CD19+TdT+MPO+CD13+CD33+	**4**	**3.5**	0.5	46,xx,t(8;21)
4	F, 34	67.6	86	M0	CD3+TdT+CD7+MPO+CD13+	**3**	0.5	**3**	46,xx,t(3;7)(p13;q32)
5	M, 55	67.6	88	L2	CD79a+CD3+CD2+CD5+CD7+MPO+CD117+CD33+	**4**	2	**4.5**	Ø, /FISH Ph-/
6	M, 29	4.9	90	L2	CD19+CD3+CD5+TdT+CD7+MPO+CD13+	**3**	1.5	**4**	46,xy
7	M, 45	83.2	60	M0	CD79a+CD19+CD10+MPO+CD13+CD33+	**4**	**4**	1	Ø, /FISH Ph+/
8	M, 29	6.4	93	UD	CD3+TdT+CD7+MPO+CD13+CD117+	**4**	0	**3**	46,xy
9	F, 28	296	79	M0	CD79a+CD3+CD5+CD7+CD117+CD13+CD33+	**3**	2	**3.5**	Ø
10	F, 64	25.6	82	L2	CD79a+TdT+MPO+CD117+CD13+	**4**	**2.5**	0.5	90,xy
11	M, 65	190	90	UD	CD19+CD10+CD20+TdT+MPO+CD33+	**3**	**3.5**	1.5	46,xy(t9;22)
12	F, 16	7.4	66	L2	CD79a+CD10+TdT+MPO+CD13+CD33+	**4**	**3.5**	1.5	Ø, /FISH Ph-/
13	M, 55	0.9	59	UD	CD79a+CD3+CD5+CD7+MPO+CD117+CD33+	**4**	2	**3.5**	86-92,xy/46,xy
14	M, 37	8.1	87	UD	CD79a+CD19+CD10+TdT+CD3+CD2+	0	**4.5**	**4.5**	46,xy,del 9p (p22), add 11q,del 12p (p13),-13, 18p?del20q(q12-qter),+1 mar
15	M, 34	9.6	74	L2	CD79a+cIgM+CD19+CD10+TdT+MPO+CD13+	**3**	**6.5**	1.5	46,xy,t(9;22)
16	M, 53	16.4	95	M1	cCD22+TdT+CD3+MPO+CD13+CD33+CD14+	**4.5**	**2.5**	**2.5**	48,xy,+8+10
17	F, 30	9.6	90	M1	CD3+TdT+CD7+MPO+CD13+CD33+	**4**	0.5	**3**	47,xx,+ mar
18	M, 45	49.5	65	M5a	CD79a+TdT+CD3+CD7+MPO+CD117+CD13+	**4**	**2.5**	**3**	Ø, /FISH Ph-/
19	M, 74	29.11	34	M0	CD79a+cCD22+TdT+CD117+CD13+CD33+	**3**	**4.5**	0.5	46,xy
20	M, 58	11.8	80	M1/M4	CD3+CD5+TdT+MPO+CD117+CD33+	**4**	0.5	**3.5**	84-90,xy
21	M, 47	14.2	51	UD	CD79a+cCD22+CD19+CD10+MPO+CD13+CD33+	**4**	**6**	1	Ø, /FISH Ph+/

BM: bone marrow; UD: undifferentiated cytomorphology; [a]positive scores are in bold; My: myeloid; B: B-lymphoid; T: T-lymphoid; Ø: conventional cytogenetic analysis failed.

Table 2. Treatment regimens and outcome.

Patient	Treatment Type[a]	CR	SCT	Outcome
1	LD	NA	No	Dead at 2.4 mo., AD
2	ALL	Yes	Auto	Dead at 51.8 mo., AD
3	AML	Yes	Auto	Alive at 14.2 mo., 1CR
4	AML	Yes[b]	Auto	Dead at 30.3 mo., AD
5	LD	NA	No	Dead at 7.1 mo., AD
6	ALL	Yes	Auto	Dead at 8.3 mo., AD
7	AML	No	No	Dead at 1.6 mo., AD
8	AML	No	No	Dead at 2.9 mo., AD
9	AML	No	No	Dead at 1 mo., AD
10	AML	Yes	No	Dead at 1.3 mo. 1CR
11	ALL	Yes	No	Dead at 6.4 mo., AD
12	ALL	Yes	Auto	Alive at 108 mo., 1CR
13	ALL	Yes	Auto	Alive at 74.4 mo, 2CR
14	ALL	Yes	No	Aliv at 101,7 mo., 1CR
15	ALL	Yes	MUD[c]	Dead at 25.7 mo., AD
16	AML	Yes	Auto	Dead at 33.7 mo., AD
17	ALL	Yes	No	Dead at 14.1mo., AD
18	AML	No	No	Dead at 22.3 mo., AD
19	LD	NA	No	Dead at 3 mo., AD
20	AML	Yes	No	Alive at 12.4 mo., 1RL
21	ALL	Yes	No	Dead at 2.1 mo., AD

LD: low dose; CR: complete remission; SCT: stem cell transplantation; MUD: matched unrelated donor; mo.: months; AD: active disease; RL: relapse; [a]Low dose or induction treatment according to the EORTC AML10, AML12 or ALL 4 protocols;11,12,13 [b]After 3 cycles of chemotherapy; [c]In second remission.

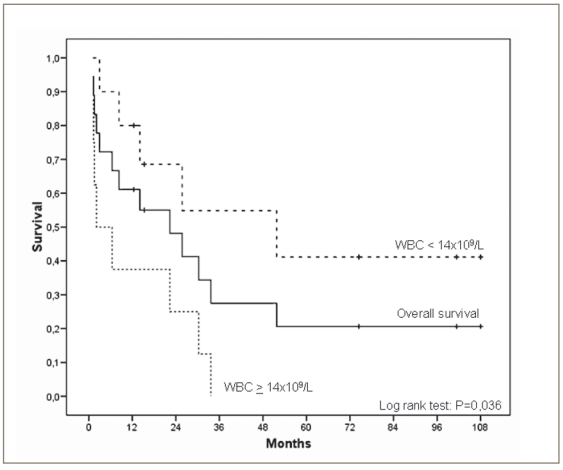

Figure 1. Overall survival and survival according to WBC <14×10^9/L and >14×10^9/L for BAL patients.

gene were negative in all of the eleven patients tested for them.

According to the EGIL classification, there were ten cases of myeloid+B-lymphoid leukemia (47, 6%), eight cases of myeloid+T-lymphoid (38, 1%), one case of B+T-lymphoid (4, 8%) and two cases of trilineage myeloid+B+T-lymphoid leukemia (9, 5%). The most common phenotypic feature was the expression of CD34 antigen which was positive in 20/21 patients.

CR achievement rate was 72% with first-line high-dose chemotherapy and the median follow-up is 74.4 months (range, 12.4-108.1). Median disease-free survival was 21.2 months (95% CI, 1.5-41.3) and the overall survival probability at 2 and 5 years 48% and 21%, respectively. Five patients are alive–three in first complete remission (CR), one in second CR, and one in first relapse; sixteen patients died - fifteen due to active disease and one from toxicity. Patients that received ALL-tailored chemotherapy had a better CR achievement rate (100%) over the patients that received AML-tailored chemotherapy (60%) (P=.007) (Table 3), but there was no difference in survival. Out of all the parameters tested for their impact on survival, only WBC count < or > 14×10^9/L (median) was found to have statistically significant impact (P=.036) (Figure 1). Fisher's exact test was used to test the difference in types of chemotherapy and phenotype subtypes (myeloid+B-lymphoid vs. myeloid+T-lymphoid) between the groups with low and high WBC counts. Although more patients received ALL-tailored chemotherapy in the group with WBC count <14×10^9/L (70 vs. 25%), the two groups did not differ significantly in their distribution according to the choice of chemotherapy (P=.1534) or phenotype subtypes (P=.2867). Also, there was no difference in CR rates or survival between the patients classified as ALL or AML, nor between the two subtypes of BAL-myeloid+B-lymphoid vs. myeloid+T-lymphoid subtype. There was no advantage in survival in patients who underwent autologous SCT.

DISCUSSION

BAL is a rare form of acute leukemia recognized by the WHO classification of hematologic malignancies.[2] Its definition is based on immunophenotyping, and EGIL scoring system is used to distinguish BAL from other leukemia that co-express markers from different lineages.[1] Studies attempting further molecular stratification of BAL have also been performed,[15] one of them being the analysis earlier performed in our institution, in which immunoglobulin heavy chain (IgH) and T-cell receptor γ (TCRγ) gene rearrangements were found to correlate well with lymphoid BAL morphology, whereas

cyclin A1 (CycA1) expression correlated with myeloid and undifferentiated morphology of BAL.[16] Being a rare entity, it is of no surprise that the publications concerning BAL mostly involve single-center experiences or case-reports and the recently published study on 43 BAL patients by the Korean Society of Hematology AML/MDS working party is among the ones with the highest number of patients.[17] The reported patient outcomes range from 8.1% at four years to close to 60% at five years.[5,8,9,11,17] So far, no treatment has been designed uniquely for BAL and attempts in improving the outcome are being made also by implementation of novel drugs, such as nelarabine for BAL patients with T cell markers.[18]

The incidence of BAL diagnosed in our Center (3.9%) corresponds to the literature data, as well as the distribution of patients within the four subtypes-myeloid+B-lymphoid and myeloid+T-lymphoid being the most frequent. The high frequency of CD34 expression and the diverse cytologic findings support the suggestion that BAL arises in a multipotent progenitor-cell. The cytogenetic findings were miscellaneous and Ph chromosome was positive in 4 out of 20 patients, which is lower than previously reported (30-35%).[5,6] 11q23 abnormalities were observed in none of the eleven patients tested, contrary to what would be expected. Treatment decisions in this group of patients were mainly based on cytology and ALL-designed treatment had an advantage in the achievement of CR without the advantage in survival, as was already reported by Aribi et al.[9] The low rate of allogeneic SCT is attributable to the fact that patients lacked sibling donors. The overall survival was poor with only 21% of patients surviving 5 years.

According to the literature, unfavorable prognostic findings are age and the occurrence of the abnormalities involving 11q23 or the Ph chromosome,[5] to which the WBC count has been added lately.[9] This was confirmed in our study, where patients with a WBC count $>14\times10^9$/L had shorter overall survival than patients with lower WBC counts. The three Ph-positive patients in our study did have a poor outcome with OS ranging from 1.6-25.7 months, but due to a small number no definite conclusions can be made about the prognostic impact of the Ph chromosome. The Korean group identified myeloid+T-lymphoid phenotype as having a bad prognostic impact and was first in suggesting that immunophenotype in BAL has prognostic implications.[17] Our failure to identify any differences in outcome between the four BAL subtypes can possibly be attributed to the smaller number of patients analyzed.

Based on our results, as well as the early reports on

Table 3. Patients and disease characteristics (n=21).

M/F ratio	16/5
Age (years), median (range)	44 (16-74)
Laboratory values	Median (range)
Bone marrow blasts (%)	82 (34-95)
WBC ($\times10^9$/L)	14,2 (0,9-296)
Hgb (g/L)	101 (47-149)
Plt ($\times10^9$/L)	149.5 (7-285)
FAB	n
ALL	6
AML	9
Undifferentiated	6
Immunophenotype	
B+My	10
T+My	8
B+T+Iy	1
B+T+My	2
Karyotype (n=15)[a]	
Normal	4
Numeric changes	5
Structural changes	5
Complex changes	1
Philadelphia chromosome[b]	4
Chemotherapy protocols	
AML-tailored	8
ALL-tailored	10
Low-dose chemo.	3
CR achieved with int. chemo.	13 (72%)
SCT	
Autologous	7
Allogeneic (MUD)	1
Survival	Median (95%CI)
DFS (months)	21.2 (1.5-41.3)
OS at 2 and 5 years	48 and 21%

MUD: matched unrelated donor; DFS: disease-free survival; OS: overall survival; [a]Number of patients in which conventional cytogenetics was successfully done; [b]G-banding or FISH.

BAL, one would assume that the prognosis of BAL remains poor; however, two recently published papers report different conclusions. In the above mentioned study by Aribi et al, the overall survival probability at five years was reported to be close to 60%. Still, the Ph chromosome positive patients, which would be considered high-risk, were excluded from the study. Additionally, only one fourth of the patients met the EGIL criteria, and for the rest the criteria according to which a somewhat lower score was needed to consider a lineage involved were used. Nevertheless, there was no difference in survival between the two groups of patients.[9] In the article by Lee et al a five year overall survival of 54% was reported. However, the analysis was done on only eight patients with median follow up of 10.5 months. Also, in none of the patients the EGIL criteria were fully met.[11]

In conclusion, BAL patients should be regarded as high-risk. In adittion, we have confirmed that a higher WBC count is an adverse prognostic feature. Since current treatment approach is heterogeneous and often based on cytomorphology, treatment protocols designed specifically for this type of leukemia should be devised, bearing in mind that ALL-designed protocols may have a better response rate. The role of allogeneic SCT, including MUD, especially for patients with adverse prognostic features should be established. The use of novel drugs, such as nelarabine for BAL patients with T cell markers or tyrosine kinase inhibitors for Ph positive BAL patients should also be addressed.

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