

Biphenotypic Acute Leukemia Treated With Acute Myeloid Leukemia Regimens: A Case Series

Songul Serefhanoglu, MD; Yahya Buyukasik, MD; Hakan Goker, MD; Nilgun Sayinalp, MD; Osman I. Ozcebe, MD

This study retrospectively analyzed 8 cases of biphenotypic acute leukemia (BAL) in respect of morphology, immune phenotype, karyotype, and clinical manifestations. Six patients had myeloid plus T lymphoid, and 2 cases had myeloid plus B-lymphoid immune phenotypic markers. Because selection of an antileukemic chemotherapy regimen for acute leukemia is largely based on whether a case is classified as myeloid or lymphoid, the presence of markers for both lineages may have important implications for treatment. However, there is no consensus yet on chemotherapy for patients with BAL. All of our patients were treated with regimens designed for acute myeloid leukemia (AML). Five patients were treated with high-dose cytarabine plus mitoxantrone and 3 achieved complete remission. Two patients treated with idarubicin plus cytarabine. Both of them achieved complete remission. One case was given cytarabine plus mitoxantrone and achieved complete remission. Consequently, 6 out of 8 BAL patients achieved complete remission with AML-type regimens.

Keywords: leukemia ■ genetics ■ immunology ■ treatment

J Natl Med Assoc. 2009;101:270-272

Author Affiliations: Department of Internal Medicine, Division of Hematology, Hacettepe University Hospital, Ankara, Turkey.

Corresponding Author: Songul Serefhanoglu, MD, Hacettepe University Hospital, Department of Internal Medicine, Division of Hematology, Samanpazari, Ankara, 06030, Turkey, GSM (dr.songul1978@yahoo.com).

INTRODUCTION

Most cases of acute leukemia can be classified as myeloid or lymphoid by standard light microscopy morphology and cytochemistry and a comprehensive panel of immunological markers that detect antigens in the membrane or cytoplasm of myeloid and B- and T-lymphoid cells. Biphenotypic acute leukemia (BAL), a rare type of leukemia, represents about 5% of cases of adult acute leukemia.¹ Acute leukemias are broadly classified as myeloid or T and B lymphoid according to the morphological fea-

tures as well as the surface and/or cytoplasmic antigen expression of proliferating blasts.¹ Based on a previously described scoring system, the European Group for Immunologic Classification of Leukemia (EGIL) proposed a set of diagnostic criteria for BAL.² This scoring system is based on the number and degree of the specificity of certain markers for myeloid or T- and B-lymphoid blasts. The leukemic cells from patients with BAL most commonly coexpress B-lymphoid and myeloid markers and, less frequently, T-lymphoid and myeloid markers.³ The World Health Organization (WHO) has adopted the EGIL revised criteria for BAL with 1 notable difference; in the WHO criteria, the total score required for myeloid or lymphoid lineages is ≥ 2 , rather than > 2 used in the EGIL criteria.

Whether patients with BAL should be treated with regimens designed for acute myeloid leukemia (AML), acute lymphoid leukemia (ALL), or both remains unclear. More importantly, the optimal therapy is unknown. Currently, there is no universal treatment approach for patients with BAL. ALL regimens appeared to be more effective for achieving a complete remission than AML regimens (78% vs 57%, respectively).¹ We identified 8 BAL patients who were treated with AML regimens. In contrast to the literature, the majority of our patients coexpressed T-lymphoid and myeloid markers.

PATIENTS, METHODS, AND RESULTS

All patients had been diagnosed at Hacettepe University Hospital. The median age of the patients at diagnosis was 44.8 years (range, 24-64). The male to female ratio was 7:1. The median white blood cell (WBC) count, hemoglobin concentration, and platelet count were $16 \times 10^9/l$ (range, $1.6-50 \times 10^9/L$), 81 g/L (range, 50-100 g/l), and $66.1 \times 10^9/L$ (range, $15-209 \times 10^9/L$), respectively. The median follow-up duration was 18 months. For flow cytometric studies, bone marrow mononuclear cells were isolated by ammonium chloride hypotonic solution and incubated at room temperature for 20 minutes with 100 $\mu\text{g/mL}$ of immunoglobulin to prevent nonspecific

binding. HLA-DR, MPO (myeloperoxidase), CD13, CD33, CD34, CD14, CD15, CD117, CDW65, CD2, CD3, CD5, Tdt, CD7, CD10, CD20, CD19, CD22, κ , and λ expressions were evaluated by flow cytometry. Cell populations were considered positive for a particular marker if more than 20% of the cells were stained with the antibody. The diagnosis of mixed lineage leukemia (BAL) was based on the EGIL classification.⁴ Cytogenetic studies comprised standard G-banding karyotypic analysis, and morphology examination was performed on Wright-stained marrow aspirate and peripheral blood smears.

Two patients (25%) coexpressed B-lymphoid (B) and myeloid markers (M), and 6 patients (75%) coexpressed T-lymphoid (T) and myeloid markers. Seven patients had de novo acute leukemia; one represented transformation from myelodysplastic syndrome. All patients were treated with AML regimens, and 6 patients achieved a complete remission (CR). The treatment regimens and

responses, and immunophenotypic profiles of the cases are shown in Table 1 and Table 2, respectively.

DISCUSSION

In rare acute leukemia cases, blastic cells (blasts in marrow) may express markers of more than 1 lineage or myeloblast; B and T lymphoblasts may be present simultaneously. There has been a trend to classify these entities separately as biphenotypic and biclonal acute leukemias, respectively. However, both EGIL and WHO classifications have sorted these disorders under the name BAL.⁵ Most studies report that 70% of BAL cases have M+B phenotype, whereas only 23% to 33% have M+T phenotype. The M+B+T and B+T phenotypes are very rare.

Clinically, BAL manifests with the usual features of AML. The CR rates for BAL are variable, as are their clinical courses. Most series of BAL have shown poor outcome.⁶ Older age and presence of the Philadelphia

Table 1. Clinical and Cytogenetic Data

Case	Diagnosis	Age (Years) / Sex	WBC x 10 ³ / μ	Karyotype	First Therapy	Response
1	T-myeloid	48 / Female	13	46,XX[20]	HAM	CR
2	T-myeloid	57 / Male	20	46,XY[16]	IA	CR
3	B-myeloid	42 / Male	50.5	N/A	HAM	NA
4	B-myeloid	37 / Male	8.5	46,XY[11]	HAM	CR
5	T-myeloid	33 / Male	2.3	46,XY,t(1;9)[5]/46,XY[10]	HAM	CR
6	T-myeloid	24 / Male	14.7	46,XY [11]	HAM	NR
7	T-myeloid	64 / Male	20	46,XY del(7)[7]/46,XY[12]	IA	CR
8	T-myeloid	54 / Male	1.6	46,XY[15]	AM	CR

Abbreviations: CR, complete remission; HAM, high-dose cytarabine plus mitoxantrone; IA, idarubicin plus cytarabine; NA, not applicable; WBC, white blood cell

Table 2. Immunophenotypic Profiles of Biphenotypic Acute Leukemia Cases by Flow Cytometric Analysis

Cases	% Marrow													
	Blast	%M	%T	%B	MPO	CD13	CD33	CDW65	CD14	CD15	CD117	CD3	CD5	CD2
1	95	50	50	-	57	39	86	4	0	0	33	21	51	6
2	82	57	43	-	69	25	75	15	20	15	45	35	89	0
3	69	52	-	48	1	56	26	1	39	98	60	0	0	5
4	91	55	-	45	28	54	32	5	0	23	12	2	4	12
5	58	53	47	-	0	4	78	24	47	12	74	35	16	22
6	70	48	52	-	1	48	91	1	0	0	97	79	1	98
7	94	45	55	-	69	55	26	13	3	8	60	76	32	35
8	41	60	40	-	29	47	43	36	0	5	14	42	40	42

Cases	CD10	Tdt	CD7	CD22	CD19	CD20	HLA-DR	CD34
1	0	38	91	11	2	0	6	61
2	0	25	0	12	0	4	5	55
3	54	60	0	45	35	78	0	65
4	34	87	2	53	24	7	67	69
5	2	0	91	3	2	3	21	73
6	0	2	98	64	0	1	98	97
7	23	3	26	43	3	4	80	61
8	0	0	40	3	3	2	69	54

Abbreviations: B, B lymphoid; M, myeloid; MPO, myeloperoxidase; T: T lymphoid

chromosome have been identified as poor prognostic markers. The outcome of BAL in our series was poor too. Legrand et al confirmed the poor prognosis of BAL when compared to AML or ALL seen during the same period of time in terms of complete remission (47%, 62%, and 82%, respectively).⁷ Aribi et al demonstrated that hyperfractionated cyclophosphamide/vincristine/doxorubicin/dexamethasone appeared to be more effective for achieving a CR than AML regimens (78% vs 57%, respectively). However, in their study, they did not find any difference in survival between subtypes of BAL.¹

There are literature data indicating that BAL patients poorly respond to therapeutic regimens directed to AML.⁸ Although there are no uniform criteria about whether to treat these patients as ALL or AML, it is likely that an intensive approach with high-dose therapy followed by stem cell transplantation is required to eradicate the disease permanently.³ Treatment outcomes were negatively related to the expression of CD34 antigen and cytogenetic findings. The most frequent cytogenetic abnormalities described were Philadelphia chromosome and 11q23 mutations.⁹ Other published series using the EGIL definition of BAL also showed a relatively high frequency of t(9;22) and 11q23 translocation.¹⁰ However, none of our patients had this cytogenetic abnormalities.

In summary, in contrast to the literature, the majority of our patients coexpressed T-lymphoid and myeloid markers. All of our patients were treated with AML regimens, and 6 out of 8 patients achieved CR.

REFERENCES

1. Aribi A, Bueso-Ramos C, Estey E, et al. Biphenotypic acute leukaemia: a case series. *Br J Haematol*. 2007;138:213-216.
2. Bene MC, Castoldi G, Knapp W, et al. Proposals for the immunological classification of acute leukemias. European Group for the Immunological Characterization of Leukemias (EGIL). *Leukemia*. 1995;9:1783-1786.
3. Matutes E, Morilla R, Farhat N, et al. Definition of acute biphenotypic leukemia. *Haematologica*. 1997;82:64-66.
4. Bennett JM, Catovsky D, Daniel MT, et al. Proposed revised criteria for the classification of acute myeloid leukemia: a report of the French-American-British cooperative group. *Ann Intern Med*. 1985;103:620-625.
5. Greer JP, Foerster J, Lukens JN, et al. Acute Myeloid Leukemia in Adults. In: Greer JP, Baer MR, Kinney MC. *Wintrube's Clin Hematol*. 2004;2097-2113.
6. Killick S, Matutes E, Powles RL, et al. Outcome of biphenotypic acute leukemia. *Haematologica*. 1999;84:699-706.
7. Legrand O, Perrot JY, Simonin G, et al. Adult biphenotypic acute leukaemia: an entity with poor prognosis which is related to unfavourable cytogenetics and P-glycoprotein over-expression. *Br J Haematol*. 1998;100:147-155.
8. Mi Y, Bian S, Meng O, et al. Study on the clinical characteristics of biphenotypic acute leukemia. *Zhonghua Xue Ye Xue Za Zhi*. 2000;21:352-354.
9. Scolnik MP, Aranguren PN, Cuellar MT, et al. Biphenotypic acute leukemia with t(15;17). *Leuk Lymphoma*. 2005;46:607-610.
10. Carboell F, Swansbury J, Min T, et al. Cytogenetic findings in acute biphenotypic leukemia. *Leukemia*. 1996;10:1283-1287. ■