Outcomes in Patients With Mixed Phenotype Acute Leukemia in Morocco

Fatima Bachir, PhD, Jihane Zerrouk, MD,* Scott C. Howard, MD,† Omar Graoui, MD,‡ Ali Lahjouji, PhD,* Leila Hessissen, MD,§ Sanae Bennani, PhD,* Assmae Quessar, MD,‡ and Rajae El Aouad, MD**

Summary: Mixed phenotype acute leukemia (MPAL) includes biphenotypic and bilineal types of leukemia, which constitute rare subtypes that require individualized therapy. Outcomes in Moroccan patients with MPAL are unknown. Among 1264 patients with acute leukemia, 20 were classified as having MPAL, including 17 with biphenotypic acute leukemia (1.3%) and 3 with bilineal leukemia (0.2%). There were 8 adults and 12 children. In 12 cases (60%), leukemic blasts expressed myeloid and T-lymphoid antigens, and, in 5 cases (25%), leukemic blasts expressed B lymphoid antigens plus myeloid antigens. Patients were initially treated on protocols for acute myeloid leukemia (n = 4), acute lymphoblastic leukemia (ALL, n = 14), or with palliative care (n = 2). The probability of survival at 2 years in MPAL cases was 52% ± 14%. Six of the 12 patients younger than 15 years remain alive versus 1 of 8 adult patients. Patients treated with ALL-directed therapy had significantly higher overall survival than those treated with acute myeloid leukemia–directed therapy ($P = 0.003$). There was no association between the phenotypic characteristics and the clinical outcome ($P = 0.83$). In conclusion, MPAL represents 1.5% of acute leukemia in Morocco. The prognosis is poor, but initial treatment with therapy directed toward ALL, improved supportive care, and the prevention of abandonment of therapy may improve outcomes in this subgroup of patients.

Key Words: mixed phenotype acute leukemia, immunophenotype, prognosis

(*J Pediatr Hematol Oncol* 2014;36:e392–e397)

Most cases of acute leukemia can be assigned a specific lineage: acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML) according to the morphologic, cytochemical, and immunophenotypic characteristics of the blasts cells. A minority of patients with acute leukemia has immunophenotypic feature characteristics of >1 cell lineage. These cases are designated as biphenotypic acute leukemia (BAL) or bilineal leukemia. To distinguish between BAL and acute leukemia having aberrant expression of other lineages, BAL was defined according to a scoring system adopted by the European Group for the Immunological Classification of Leukemia (EGIL).[1,2] This system is based on the number and degree of specificity of the lymphoid B/T and myeloid markers expressed simultaneously by the blasts. The World Health Organization (WHO) now terms BAL mixed phenotype acute leukemia (MPAL), and the new definition is more stringent than the EGIL scoring proposal.[3] Knowledge of the biology, clinical characteristics, and outcomes of patients with mixed lineage leukemia is limited in Morocco, so we analyzed 17 patients with BAL and 3 with bilineal leukemia diagnosed during a 6-year period.

Received for publication November 14, 2012; accepted February 20, 2013.

From the *Laboratoire de cytométrie en flux, Institut National d'Hygiène; †Unité d'hémato-oncologie pédiatrique (UHOP), Hôpital d'enfants, Rabat, Maroc; ‡Service d'hématologie et oncologie pédiatrique, Hôpital, Casablanca, Maroc; and §Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN.

The authors declare no conflict of interest.

Reprints: Fatima Bachir, PhD, Institut National d'Hygiène, 27 Av. Ibn Batouta, BP 769, 10 000 Rabat, Maroc (e-mail: bachir_fatima03@yahoo.fr).

PATIENTS AND METHODS

Patients

From January 2004 to December 2010, 1264 adult and pediatric patients with newly diagnosed acute leukemia were treated at the Haematology and Paediatric Oncology services of University Hospitals of Rabat and Casablanca and were referred to the National Institute of Hygiene and the pediatric Rabat unit laboratories of Rabat for immunophenotyping. Twenty (1.5%) patients were diagnosed with de novo mixed leukemia and are the subject of this study. The Rabat and Casablanca units are the only specialized public facilities for pediatric and adult leukemia patients in Morocco. A diagnosis of ALL or AML was made according to the morphologic, cytochemical, and immunophenotypic characteristics of the blast cells.

Flow Cytometric Analysis and Diagnostic Criteria

The immunophenotype was performed on bone marrow aspirates or peripheral blood samples collected in EDTA with a panel of antibodies to leukocytes-associated markers. Immunophenotypic characterization consisted of 2 consecutive steps. The first panel included CD10, CD19, CD22, CD79a, CD3 (surface and cytoplasmic), CD7, CD13, CD33, myeloperoxidase (MPO), HLADR, CD34, terminal deoxynucleotidyl transferase, and CD45. The first panel considers the most lineage specific markers and is able to identify the lineage in the majority of leukemia cases. According to the results obtained, additional markers (secondary panel) were considered, including CD1a, CD2, CD4, CD5, CD8, CD11b, CD11c, CD14, CD36, CD61, CD41a, and CD117.

Stained cells were analyzed by flow cytometry on a 3-color FACSCalibur flow cytometer (Becton Dickinson Immunocytometry Systems) by collecting 10,000 ungated list mode events. Blasts initially were gated for analysis by using CD45 versus light side scatter. Leukemic samples were considered positive for a particular antigen if $\geq 20\%$ of leukemic cells reacted with an antibody. The diagnosis of BAL was on the basis of the first immunophenotypic

TABLE 1. Chemotherapy MARAll-06-HR National Moroccan Protocol

Prephase
Prednisone: 60 mg/m^2 divided into 2 doses each day, days 1-7
Induction
Prednisone: 60 mg/m^2 divided into 3 doses each day, days 8-21
Vincristine: 1.5 mg/m^2 days 8, 15, 22, and 29
L-Asparaginase: 6000 UI/m^2(IM): 9 injections between day 22 and day 38 (every 2 days)
Daunorubicin: 40 mg/m^2 days 8, 15, 22, 29
Consolidation
Mercaptopurine: 50 mg/m^2/d, days 1-21 and 29-49
Cyclophosphamide: 750 mg/m^2 days 1 and 15
Cytarabine: 30 mg/m^2 every 12 h subcutaneously days 1 and 2, 8 and 9, 15 and 16
Vincristine: 1.5 mg/m^2, days 29 and 43
Prednisone: 40 mg/m^2/d divided into 3 daily doses, days 29-35
Methotrexate
25 mg/m^2 dose, day 36
5000 mg/m^2 days 29 and 43
Intensification number 1
Dexaméthasone: 10 mg/m^2/d, days 1-15
Vincristine: 3 mg/m^2 IV, days 1, 8, 15
L-Asparaginase: 6000 UI/m^2 IM, days 3, 5, 7 9, 11, and 13
Doxorubicin: 25 mg/m^2 days 1, 8, 15
Mercaptopurine: 50 mg/m^2/d, days 9-49
Cyclophosphamide: 750 mg/m^2 IV, days 29 and 43
Cytarabine: 30 mg/m^2 12 h subcutaneously, days 29-30, 36-37, 43-44
Interphase
Vincristine: 1.5 mg/m^2 days 1, 15, 29, 43
Prednisone: 40 mg/m^2/d divided into 3 daily doses days 1-7, 29-36
Mercaptopurine: 50 mg/m^2/d, days 1-49
Methotrexate: 25 mg/m^2/d, days 8, 15, 22, 36,
Asparaginase: 5000 mg/m^2/d (SIV 3 h), days 1, 29, 43
Intensification number 2
Prednisone: 40 mg/m^2/d (3 doses per os), days 1-15
Vincristine: 1.5 mg/m^2 days 1, 8, and 15
L-Asparaginase: 6000 UI/m^2 IM, days 3, 5, 7, 9, 11, and 13
Daunorubicin: 30 mg/m^2 days 1, 8, 15
Mercaptopurine: 50 mg/m^2/d, days 29-49
Cyclophosphamide: 1000 mg/m^2, day 29
Cytarabine: 30 mg/m^2/injection $\times$ 2/d (SC), days 29-30, 36-37, and 43-44
Maintenance treatment
Mercaptopurine: 75 mg/m^2/d
Methotrexate: 25 mg/m^2/wk for 24 months
Vincristine: 1.5 mg/m^2 by injection on day 1
Dexamethasone: 6 mg/m^2/d in 3 doses per os, days 1-5 during the first 24 months

evaluation of the blast population; if cases had lymphoid and myeloid markers or both T-lineage and B-lineage markers, an extensive immunophenotyping was performed to support the diagnosis. The final diagnosis of BAL was made according to a scoring system adopted by the EGIL.[1,2] Initially, 26 cases were diagnosed as BAL and 3 cases as bilineal leukemia. The BAL cases were reanalyzed according to 2008 WHO classification of tumors of hematopoietic and lymphoid tissues[3] and were categorized as having MPAL, but 9 patients were not confirmed as having MPAL because of the weak expression of B markers: in 5 patients, classified as T-ALL in 3 and a diagnosis of AML in 2; 4 cases lacked the expression of MPO and were classified as T-ALL in 3 cases and as B-ALL in 1 case. Finally, 20 were classified as having MPAL, including 17 with BAL and 3 with bilineal leukemia.

Cytogenetics

Cytogenetic analysis was performed on the bone marrow by the direct preparation of unstimulated cells after 24 hours in culture at 37°C on a culture medium RPMI 1640, 1×.

The R-banding method was used to prepare metaphase cells. The karyotype was performed according to the International System of Human Cytogenetic Nomenclature 2008.[4] At least 20 mitoses were examined.

Treatment

Patients were treated with national Moroccan protocols for AML or ALL (AML-MA03 http://www.smccbm.org/fichiers_pdf/conferencesjib2009/3-JIB2009_Quessar.pdf) and Marall06 (Table 1) or LALA 94.[5] Complete remission (CR) was defined as $<5\%$ blasts in the bone marrow with recovery from cytopenias.

Statistical Methods

The Kaplan-Meier method was used to estimate the probability of overall and event-free survival. Survival analysis was performed using a SYSTAT version 12.

TABLE 2. Clinical Characteristics, Biological Features, and Immunophenotype of all Patients

Case/ Type (MPAL)	Age (y)/ Sex	White Blood Cell Count (10^9/L) at Diagnosis	Circulating Blasts (%) at Diagnosis	FAB	Extramedullary Involvement	Cytogenetics	Immunophenotype
Biphenotypic (T + Myeloid)							
1	11/M	1.7	32	M1	None	28-46 XY, + 19	CD13, CD33, CD117, MPO, cCD3, CD5, CD7, TdT, CD34, HLA-DR
2	8/F	159	95	L1	None	No metaphases seen	CD13, CD117, MPO, sCD3, cCD3, CD7, TdT, CD34, HLA-DR
3	12/F	204	53	M4	None	40-46 XX	CD13, CD33, CD117, MPO, CD2, sCD3, cCD3, CD7, CD34, HLA-DR, TdT
4	5/M	31.1	90	M1	None	Not done	sCD3, cCD3, CD5, CD7, CD13, CD33, CD117, CD34, HLA-DR
5	14/M	39.6	98	M2	None	Not done	CD13, CD33, MPO, sCD3, cCD3, CD5, CD7, CD34, HLA-DR
6	34/M	107	72	L2	None	No metaphases seen	CD1a, sCD3, cCD3, CD5, CD7, CD8, CD79a, CD33, MPO, CD34, TdT
7	10/M	3.94	0	ALL	Mediastinum	Not done	CD1a, sCD3, cCD3, CD5, CD7, CD8, CD79a, CD33, MPO, CD34, TdT
8	69/M	3.3	0	M0	None	Not done	cCD3, CD5, CD7, CD33, MPO, TdT, HLA-DR, CD34
9	46/M	6.9	0	M1	None	46 XY	cCD3, CD5, CD7, CD79a,CD33 MPO, TdT, CD34
10	8/M	291	87	L2	Mediastinum	Not done	CD1a dim, sCD3, cCD3, CD5, CD7, CD13, MPO, CD34, TdT
11*	16/M	67	98	M1	None	At diagnostic: 46-47 XY, + 5, + 9, −17, −20 (cp9)[17/17] At relapse: 49, + 4, + 5, + 9, + 19, −17, −20, + mar	CD13, CD117, MPO, cCD3, CD7, CD34, HLA-DR
Biphenotypic (B + T)							
12	2/F	6.3	0	M0	Mediastinum	46 XX	CD10, CD19, CD22, CD79a, CD2, cCD3, CD7, HLA-DR
13	40/F	140	93	M0	None	46 XX, t(6,11) (q27;q23)/45 XX, t(6,11) (q27;q23), −21	CD19, CD22, CD79a, cCD3, CD4, CD7, CD34, TdT
14	44/M	35.14	77	ALL	None	ND	cCD3, sCD3, CD5, CD7, CD8, CD19, CD22, CD79a, TdT, HLA-DR
Biphenotypic (B + Myeloid)							
15	3/M	8.9	92	L2	None	46 XY	CD13, CD33, CD117, MPO, CD10, CD19, CD22, CD79a, CD34, HLA-DR, TdT
16	23/M	2.4	96	L2	None	46 XY	CD13, CD33, MPO, CD19, CD22, CD79a, CD34, HLA-DR
17	8/F	11	0	ALL	None	No metaphases seen	CD10, CD19, CD22, CD79a, CD33, MPO, CD34, TdT
Bilineal (B + Myeloid)							
18	55/F	1.5	0	M5a	None	49 XX + mar1 + mar2, mar3(9/20)/46 XX(11/20)	CD11b, CD13, CD14, CD33, CD36, MPO, HLA-DR/CD19, CD22, CD79a, CD33, CD34, HLA-DR, TdT
19*	4/F	114	88	L1	None	Not done	CD11c, CD15, CD13, CD33, MPO/CD19, CD22, CD79a, CD33, CD34, HLA-DR
Bilineal (T + Myeloid)							
20	11/M	5	0	L2	None	46 XY/86-92(2N), XXYY/45 XY	cCD3, sCD3, CD5, CD7, CD33, CD34, HLA-DR/CD7, CD11b, CD11c, CD33, CD34, CD117, HLA-DR

*Cases 11 and 19 are secondary leukemia.
F indicates female; FAB, French–American–British; M, male; MPAL, mixed phenotype acute leukemia.

TABLE 3. Treatment and Outcome of Patients With Mixed Lineage Leukemia

Cases	Treatment	CR	CR Duration	First Event	Time to First Event (y)	Survival After Diagnosis (y)
1	AML-MA03	Yes	0.42	Relapse	0.50	0.79
2	MARALL-06	Yes		Continuous CR		5.35
3	AML-MA03	Yes		Death in remission†	0.20	0.20
4	MARALL-06	Induction death		Early death†	0.08	0.08
5	MARALL-06	No response		Death	0.09	0.13
6	MARALL-06	Yes		Continuous CR		2.12
7	MARALL-06	Yes		Continuous CR		1.64
8	Palliative mercaptopurine	No response		Death	1.56	1.56
9	Palliative hydroxyurea	Yes		Death	1.30	1.30
10	MARALL-06	Yes		Continuous CR		1.07
11	MARALL-06	No response		Death	0.16	0.16
12	MARALL-06	Yes		Continuous CR		3.85
13	LALA-94	Yes	0.77	Relapse	0.91	1.05
14	MARALL-06	No response		Death	0.48	0.48
15	MARALL-06	Yes		Death in remission†	0.38	0.38
16	MARALL-06	Yes	1.16	Abandonment*	0.82	1.61
17	MARALL-06	Yes		Continuous CR		1.90
18	AML-MA03	Induction death		Early death†	0.16	0.16
19	AML-MA03	No response		Death	0.06	0.06
20	MARALL-06	Yes		Continuous CR		4.13

*Abandoned treatment at day 29 of the interphase and relapsed 4 months later.
†Death from toxicity.
CR indicates complete remission.

RESULTS

Patient Characteristics

Among the 1264 adult and pediatric patients (511 female and 753 male patients) with newly diagnosed acute leukemia, 610 had B-lineage ALL, 225 had T-lineage ALL, 409 had AML, 17 had BAL (1.3%), and 3 had bilineal leukemia (0.2%), and so a total of 20 had MPAL and were included in this study.

Of the 17 BAL patients, 16 cases were de novo and 1 was secondary BAL (case 11; whose original disease was AML). For bilineal patients, 2 cases were de novo and 1 was secondary (case 19; whose original disease was ALL). Clinical and biological features of the patients are summarized in Tables 2 and 3. The patients ranged in age from 1 to 69 years (median, 11.5 y). There were 13 male and 7 female patients, including 12 children and 8 adults. Three of the pediatric patients had a mediastinal mass. The white blood cell count was moderate to high (mean, 63×10^9/L) and circulating blasts were usually present. According to French–American–British criteria, 11 had morphology resembling AML and 9 were consistent with ALL.

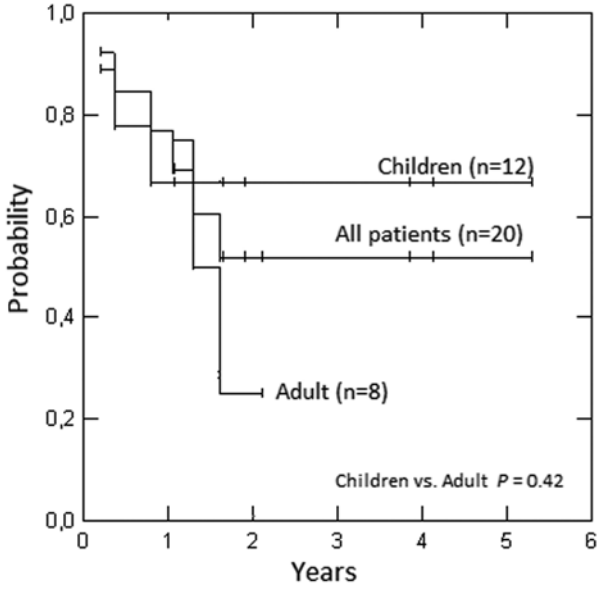

FIGURE 1. The Kaplan Meier plot of overall survival for adult and children with mixed phenotype acute leukemia leukemia.

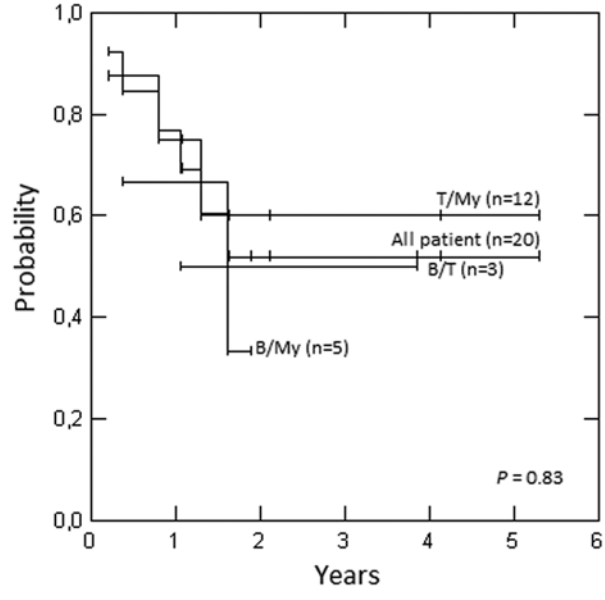

FIGURE 2. The Kaplan Meier plot of overall survival according to phenotype in mixed phenotype acute leukemia patients.

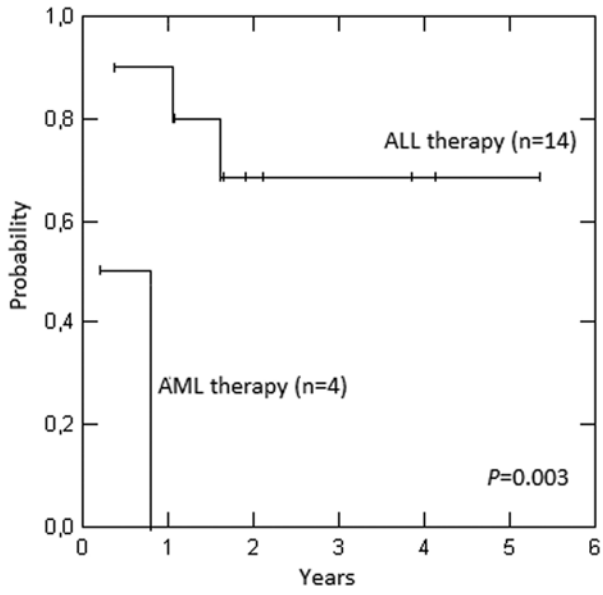

FIGURE 3. The Kaplan Meier plot of overall survival according to initial therapy in mixed phenotype acute leukemia patients.

Immunophenotyping

The immunophenotype of all patients is shown in Table 2. In BAL patients, double staining confirmed the coexpression of lymphoid and myeloid markers in a variable proportion of blasts. In addition, 3 cases had 2 distinct lymphoid B or T and myeloid populations and were classified as bilineal leukemia. The majority of cases expressed early hematopoietic markers, such as CD34 (90%) and class II HLA-DR determinants (74%). For patients with myeloid lineage disease, the most frequent positive markers were MPO, CD33, CD13, and CD117 in 88%, 76%, 70%, and 47% of cases, respectively. For B lymphoid lineage, all patients expressed CD19, CD22, and CD79a and 50% expressed CD10. All T-lineage patients were positive for cCD3 and CD7, 47% showed a weak expression of sCD3, and none of them expressed CD4. The expression of the other T-lymphoid markers was as follows: CD5 was 67%, CD1a was 21%, and CD8 was 14%.

Cytogenetic Abnormalities

Cytogenetic analysis was successfully carried out in 10 patients (Table 2). A normal karyotype was found in 4 cases (40%), whereas clonal abnormalities were seen in 6 cases (60%). One had an abnormality in 11q23, another had a complex karyotype, and 2 were hypodiploid.

Treatment and Outcome

The initial chemotherapy regimens and clinical outcome are summarized in Table 3. In the 4 patients who received AML therapy, 2 BAL patients achieved CR, 1 showed no response, and 1 patient with bilineal leukemia died of toxicity. In the 14 patients who received ALL therapy initially, 10 patients achieved CR (71%), 3 showed no response, and 1 died of toxicity. The other 2 patients were given palliative treatments (cases 8 and 9): 1 treated with palliative single-agent mercaptopurine showed no response and 1 achieved CR after treatment with hydroxyurea monotherapy. Neither of the patients with secondary leukemia achieved CR and both died of progressive leukemia at 0.7 and 2 months from diagnosis (cases 19 and 11).

Overall, 13 patients entered CR (65%, 13/20) after initial induction therapy. Of patients achieving CR after induction therapy, the relapse rate was higher in adults than in children: 2 of 3 adults and only 1 of 8 children relapsed. All relapsed cases died of disease. Two CR patients died of chemotherapy toxicity. Overall, 13 patients died (65%, 13/20): the cause of death was chemotherapy toxicity in 4 patients, relapse in 3, and resistant disease in 6 patients. At last follow-up, 7 of the 13 patients achieving CR were still alive and were in remission after treatment for ALL, among whom, 6 were below 15 years of age.

The survival of patients with de MPAL is shown in Figure 1. The median follow-up was 11.04 months (range, 0.72 to 64.2 mo) and median survival time was 19.3 months. The probability of survival at 2 years is 52% ± 14%. Patients initially treated with ALL-directed therapy had better outcomes than those treated initially with AML-directed therapy ($P = 0.003$, Fig. 2). There was no significant difference in survival between children and adults [67% ± 16% (n = 13) vs. 25% ± 22% (n = 7), $P = 0.42$] or between patients with different immunophenotypes (Fig. 3).

DISCUSSION

Mixed-lineage leukemia represents an uncommon and heterogenous disease. BAL represents an important subgroup from this category and generally accounting for < 5% of acute leukemia using the EGIL scoring system.[6–8] In this study, the incidence of BAL is 1.3% and 0.2% for bilineal leukemia. This incidence is in agreement with the studies fulfilling the new criteria of the WHO classification.[9–11]

We identified 17 cases of BAL and the majority are those with myeloid and T-lymphoid phenotype (11/17, 64.7%). This frequency is higher than that in previous studies[6–8] but is in agreement with the series with the WHO criteria.[10,11] The cases coexpressing B-lymphoid and T-lymphoid markers (3/17, 17.6%) are higher than those reported in the literature.[6,9–12] The differences observed are probably due to the high frequency of T-ALL phenotype in our population.[13,14] The expression of surface CD3 was observed in the majority of our cases (9/15, 63%).

Six of 10 cases with successful cytogenetic analysis had chromosome abnormalities, including 3 with unfavorable karyotypes. The cytogenetic studies available in BAL[6,8,10–12,15,16] and bilineal leukemia[11,17] had shown a high incidence of clonal abnormalities and unfavorable karyotypes.[6,15,16]

The optimal treatment for patients with mixed-phenotype leukemia is unknown, but ALL regimens are usually effective and remain our standard initial therapy.[6,10–12] Data in response to the therapy and outcome show that our cases seemto respond to either AML or ALL induction therapy, and there was statistical difference when comparing patients according to initial therapy ($P = 0.003$)—ALL-directed treatment seems to be more effective.

Pediatric cases have been found to have better prognostics when compared with adults, but were inferior when compared with children having ALL.[6,11,12] This is consistent with our series, in which 6 of 12 children survived but only 1 of 8 adults survived. In addition, as demonstrated by previous studies[6,11,12] no apparent association was seen between the phenotypic characteristics of our patients and clinical outcome.

In conclusion, MPAL represents 1.5% of acute leukemia in Morocco. BAL represents the most frequent subgroup from this category and has a poor prognosis in both children and adults. Initial treatment with therapy directed toward ALL, improved supportive care, and prevention of abandonment of therapy may improve outcomes for this subgroup of patients.

REFERENCES

1. Béné 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.
2. Béné MC, Bernier M, Casasnovas RO, et al. The reliability and specificity of c-kit for the diagnosis of acute myeloid leukemias and undifferentiated leukemias. The European Group for the Immunological Classification of Leukemias (EGIL). *Blood*. 1998;92:596–599.
3. Varadim JM, Thiele Jüergen T, Arber DA, et al. The 2008 revision of the world Health Organisation (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood*. 2009;114:937–951.
4. Shaffer LG, Slovak ML, Campbell LJ, Karger Basel S, Jaffe ES, Harris NL, Stein H, Vardiman JW, eds, SCN. *An International System for Human Cytogenetic Nomenclature*. Switzerland: Karger; 2009.
5. Thomas X, Boiron J-M, Huguet F, et al. Outcome of treatment in adults with acute lymphoblastic leukemia: analysis of the LALA-94 trial. *J Clin Oncol*. 2004;22:4075–4086.
6. Killick S, Matutes E, Powles RL, et al. Outcome of biphenotypic acute leukemia. *Haematologica*. 1999;84:699–706.
7. Rubio MT, Dhedin N, Boucheix C, et al. Adult T-biphenotypic acute leukaemia: clinical and biological feature and outcome. *Br J Haematol*. 2003;123:842–849.
8. Owaidah TM, Al Beihany A, Iqbal MA, et al. Cytogenetics, molecular and ultrastructural predictive for lineage discrimination. *Am J Clin Pathol*. 2002;117:380–389.
9. Xu X-Q, Wang J-M, Lu S-Q, et al. Clinical and biological characteristics of adult biphenotypic acute leukemia in comparison with that of acute myeloid leukemia and acute lymphoblastic leukemia: a case series of a Chinese population. *Haematologica*. 2009;94:919–927.
10. Al-Seraihy AS, Owaidah TM, Ayas M, et al. Clinical characteristics and outcome of children with biphenotypic acute leukemia. *Haematologica*. 2009;94:1682–1690.
11. Rubnitz JE, Onciu M, Pounds S, et al. Acute mixed lineage leukemia in children: the experience of St. Jude Children's Research Hospital. *Blood*. 2009;113:5083–5089.
12. Matutes E, Pickl WF, van't Veer M, et al. Mixed phenotype acute leukemia (MPAL): clinical and laboratory features and outcome in 100 patients defined according to the WHO 2008 classification. Pre-published online Jan 12, 2011; doi:10.1182/blood-2010-10-314682.
13. Bachir F, Bennani S, Lahjouji A, et al. Characterization of acute lymphoblastic leukemia subtypes in Moroccan children. *Int J Pediatr*. 2009;2009:674801. [Epub July 19, 2009].
14. Dakka N, Bellaoui H, Khattab M, et al. Immunologic profile and outcome of childhood acute lymphoblastic leukemia (ALL) in Morocco. *J Pediatr Hematol Oncol*. 2007;29:574–580.
15. 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.
16. Carbonell F, Swansbury J, Min T, et al. Cytogenetic findings in acute biphenotypic leukaemia. *Leukemia*. 1996;10:1283–1287.
17. Weir EG, Ali Ansari-Lari M, Batista DA, et al. Acute bilineal leukemia: a rare disease with poor outcome. *Leukemia*. 2007;21:2264–2270.