



CD7/CD56 Double-Positive Acute Myelogenous Leukemia

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ABSTRACT

The continuing evolution of diagnostic concepts has been extending the disease spectrum of acute myelogenous leukemia (AML). Some reports have described a high incidence of extramedullary manifestation and significantly shorter survival of patients with CD7/CD56 double-positive AML. Thus, the reports of 12 cases of myeloid/natural killer (NK)-cell precursor phenotype AML diagnosed between July 1995 and March 1998 were reanalyzed (5 men and 7 women, 30 to 85 years old, median age 57.9 years). Extramedullary involvement was evident at initial presentation in 4 cases, 6 of the patients had high leukocyte concentrations ($>30 \times 10^9/L$), and, at the time of presentation, the majority of patients (11 of 12) had circulating blasts. According to the French-American-British classification, 5 cases were classified as M0 or M1. Expressions of CD13/CD33/CD65 as well as MPO⁺/LF⁻ blasts were classified as AML. As revealed by Southern blotting, 5 of the 12 patients presented a germline configuration for the T-cell receptor β , γ , and δ genes and for the genes coding for Ig heavy chain and Ig κ gene. Other NK-cell, T-cell, and B-cell markers were negative as well. Five patients were successfully treated with aggressive induction chemotherapy for AML (cytarabine and anthracycline) and achieved complete or partial remission, whereas 7 patients were refractory to induction chemotherapy. The median overall survival was 4.5 months. The data suggest that AML of the myeloid/NK-cell precursor phenotype constitutes a distinct biologic and clinical disease. It seems to be important to distinguish CD7⁺/CD56⁺ AML from other subtypes of AML for the development of therapeutic approaches. *Lab Hematol.* 1999;5:115-120.

KEY WORDS: Adhesion molecules · AML · CD7
· CD56

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INTRODUCTION

Exact diagnosis of acute myelogenous leukemia (AML) requires detailed information on morphology, immunophenotype, and chromosomal alterations [1]. Karyotypic abnormalities such as t(8;21) and t(15;17) are of prognostic importance to clinical outcome [1]. Immunophenotyping identifies lineage specificity and stage of maturation [2]. One of the so-called pan-T-cell antigens most expressed by AML blasts is CD7, which appears at a very early stage of maturation and is thought to originate from the immature hematopoietic stem cells [3]. This subtype has been described as CD7⁺ AML and is associated with leukocytosis, low response to chemotherapy, and poor prognosis.

Expression of CD56 is a rare phenomenon in lymphoid malignancies and is usually restricted to malignancies of T/natural killer (NK)-cell origin [4]. In AML, CD56 expression has been identified in ~20% of all cases [4] and is generally associated with cytogenetic abnormalities such as t(8;21) or trisomy 8 [4,5]. Because the CD56 antigen has been found to correspond to a neural cell adhesion molecule, its expression in leukemia or lymphoma cells is thought to play an important role in their extranodal localization [6,7,4].

The coexpression of the T/NK-cell antigens CD7/CD56 has been described in leukemias and lymphomas as NK-cell leukemia/lymphoma and as blast crisis of chronic myelogenous leukemia, or in association with Epstein-Barr virus infection [8-11]. Recently, Suzuki et al published a series of 7 cases of CD7⁺/CD33⁺/CD34⁺/CD56⁺ and frequently human leukocyte antigen (HLA)-DR⁺ acute leukemia of conceivable myeloid and NK-cell precursor phenotype [10]. All patients had an extramedullary involvement, represented by peripheral lymphadenopathy or mediastinal bulk masses. On the other hand, CD56 is identical to a neural cell adhesion molecule and is expressed mainly on neural tissues [12].

Hatano et al [6] reported the rare case of AML as an intracranial myeloblastoma in which the blasts expressed CD7/CD56. Thus, 12 cases of AML of conceivable myeloid/NK-cell precursor phenotype (ie, CD7/CD13/CD33/CD38/CD56/HLA-DR) with no NK-cell, T-cell, or B-cell marker were reanalyzed. At presentation, the majority of patients (11 of 12) had peripheral blasts, and

extramedullary involvement was evident as a primary symptom in 4 cases. Most of the patients were refractory to induction therapy (cytosine arabinoside [Ara-C] and anthracycline), and the median overall survival was 4.5 months.

MATERIALS AND METHODS

Patients

During a period of 4 years (1995-1998), 12 cases of CD7/CD56 double-positive myeloid/NK precursor acute leukemia were diagnosed. These cases (8%) were identified from 150 cases of complete immunophenotyped acute leukemias according to French-American-British (FAB) classification and the above immunologic characterization.

Morphology

Bone marrow aspirates or peripheral blood cells underwent staining with May-Grünwald-Giemsa (MG), myeloperoxidase (MPO), α -naphthol AS-D chloracetate esterase, α -naphthyl butyrate esterase, and periodic acid-Schiff (PAS). Biopsy tissues were fixed in 10% formaldehyde and embedded in paraffin. Sections were cut at 5 μ m and stained with hematoxylin and eosin, PAS, and MG.

Staining of Unseparated Whole Blood Followed by Erythrocyte Lysis for Flow Cytometric Analysis

Heparinized samples of bone marrow and peripheral blood were prepared for flow cytometric analysis using erythrocyte lysis (NH_4 -ammonium lysis reagent). The cells were first counted (Coulter Counter STKS; Coulter, Hialeah, FL) and adjusted to a concentration of $5 \times 10^3/\mu\text{L}$ using phosphate-buffered saline (PBS). Then 20 μL monoclonal antibodies were added to 100 μL of the adjusted whole-blood suspension. The suspension was incubated for 30 minutes at 4°C and vortexed every 5 minutes. After incubation with antibodies, the erythrocytes were lysed by an erythrocyte lysing reagent (Ortho-mune Lysing Reagent; Ortho Diagnostic Systems, Raritan, NJ) by incubating the suspension for 10 minutes in a tumbler. The suspension was then washed twice by centrifugation at 400g for 5 minutes with 2 mL PBS containing 0.5% bovine serum albumin (BSA) and 0.1% NaN_3 . The pellet was then resuspended in 400 μL PBS/BSA/ NaN_3 and analyzed within 30 minutes.

Monoclonal Antibodies

For 3-color staining, directly conjugated monoclonal antibodies were added simultaneously to the cells, and the suspension was incubated and washed as described above. The antibodies were prediluted between 1:2 and 1:5 with PBS after appropriate titration experiments in the FACScan flow cytometer (Becton Dickinson, Rutherford, NJ). In the present experiments, no fixative reagents were used.

The following fluorescein isothiocyanate (FITC)-conjugated monoclonal antibodies were used: CD45 (2D1, γ 1-isotype; Becton Dickinson), CD33 (WM-54, γ 1-isotype; Dako Diagnostica, Hamburg, Germany), CD38 (T16, γ 1-isotype; Dianova-Immunotech, Hamburg, Germany), CD15 (HMA, μ -isotype; Becton Dickinson), CD4 (SK3, γ 1-isotype; Becton Dickinson), CD7 (4H9, γ 2a-isotype; Becton Dickinson), and CD11c (KB90, γ 1-isotype; Dako). For the second fluorescence sources, phycoerythrin (PE)-

TABLE 1. Antibody Panel Used for 3-Color Immunophenotyping of AML*

FITC	PE	PerCP/PeCy5
CD45 (2 0 1)	CD14 (M (P 9)	CD20 (L 27)
CD34 (8 G 12)	CD38 (Hb-7)	HLA-DR (L243)
CDw65 (88 H7)	CD33 (P67.6)	CD13 (WM-47)
CD15 (MMA)	CD117 (104 D2)	CD16 (3 G 8)
CD2 (MT910)	CD14 (M ϕ P 9)	CD64 (32.2)
CD7 (4H9)	CD56 (My 31)	CD19 (SJ25C1)
MPO (H-43.5)	Lactoferrin (3C5)	

*HLA indicates human leukocyte antigen; MPO, myeloperoxidase.

conjugated antibodies were added: CD14 (MoP9, γ 2b-isotype), CD34 (8G12, γ 1-isotype), CD56 (My31, γ 1-isotype), and CD11b (D12, γ 2a-isotype) (all Becton Dickinson). As third fluorescence sources, antibodies conjugated by peridinin chlorophyll A protein (PerCP) or PE covalently labeled with cyanine 5 (PE-Cy5) were added: CD13 (WM-47, γ 1-isotype; Dako), CD3 (SK7, γ 1-isotype; Becton Dickinson), HLA-DR (L243, γ 2a-isotype; Becton Dickinson), CD16 (3G8, γ 1-isotype; Caltag Laboratories, San Francisco CA), and CD64 (32.2, γ 1-isotype, Caltag Laboratories). MPO-7 (Dako) was used for intracellular analysis of MPO after cell permeability had been increased by Ortho Permeafix (Ortho Diagnostic Systems; Dianova) [6]. The antibody panel is shown in Table 1; for more details, see Knapp et al [13].

Flow Cytometry

Flow cytometric data acquisition was performed on a FACScan by FACScan Cell Quest software. The instrument setup was standardized threefold using lymphocytes from normal subjects according to AUTComp settings (Becton Dickinson) using standardized fluorescent beads (Fluorospheres [Rainbow beads], Dako) and CD4 (SK3, γ 1-isotype; Becton-Dickinson)/CD8 (SK1, γ 1-isotype; Becton-Dickinson)/CD3 (SK7, γ 1-isotype; Becton-Dickinson) staining from lymphocytes of normal donors. The linear forward light scattering and orthogonal light scattering signals in combination with 4-decade logarithmic FITC, PE, and PerCP/PECy5 fluorescence signals were collected for 20,000 cells and stored in list mode data files.

Cytogenetic Analysis

Pretreatment bone marrow cells or peripheral blood cells were cultured in RPMI 1640 supplemented with 20% fetal calf serum without mitogens for 72 hours, incubated with colcemid at a final concentration of 0.02 $\mu\text{g}/\text{mL}$ KCl solution for 20 minutes at room temperature, and fixed with methanol:acetic acid (3:1). Chromosomes were banded using the trypsin-Giemsa method [14,1].

Southern Blot Analysis

High-molecular-weight DNA was isolated from cryopreserved leukemic cells and analyzed by Southern blotting using standard techniques. To demonstrate Ig gene rearrangements, *B γ III* and *HindIII* digests were hybridized with a 2.5-kb *EcoRI-B γ III* JH probe [5] and *BamHI* digest with a 5.7-kb *BamHI-EcoRI* Jk probe

TABLE 2. Pretreatment Presentation of Patients With Myeloid/NK Cell Precursor Acute Leukemia

No.	Age	Sex	Hb (g/dL)	Platelets ($\times 10^9$ L)	WBC ($\times 10^9$ L)	Blasts (%)	Extramedullary Involvement
1	39	F	9.1	91	171.2	91	Meningeosis leukemica
2	69	M	10.0	38	1.7	0	No
3	60	M	7.6	51	80.2	92	No
4	75	F	9.3	124	2.8	26	No
5	30	M	11.1	216	207.6	88	No
6	73	F	7.1	19	91.03	1	Meningeosis leukemica
7	59	F	11.5	70	194	98	No
8	85	F	11.4	55	6.1	14	No
9	47	M	10.8	57	1.1	21	Sulcus coronarius penis
10	66	M	9.5	43	139.1	98	No
11	39	F	10.0	47	5.9	22	No
12	53	F	9.6	55	5.3	54	Intracerebral tumor

[16]. T-cell receptor (TCR)- β genes were studied on *EcoRI* and *BamHI* digests with a 0.7-kb *BgIII-PstI* fragment containing C β 1 segments, and TCR- γ genes were investigated on *EcoRI* blots with a 1.0-kb *PstI-EcoRI* J γ 2 fragment hybridizing to both J γ 1 and J γ 2 segments. To investigate the TCR- δ gene configuration, *BgIII* and *HindIII* digests were hybridized to a 873-bp *HindIII-EcoRI* J δ 1 gene segment [14,1].

RESULTS

Clinical Features

The clinical features of the 12 patients are summarized in Table 2. Five men and 7 women, 30 to 85 years old, median age 57.9 years, were included. Six of the patients had initial high leukocyte counts ($>30 \times 10^9/L$). At time of diagnosis, circulating blast cells were observed in 11 patients and thrombocytopenia in 11 patients, and all patients were anemic (hemoglobin [Hb] <11.5 g/dL).

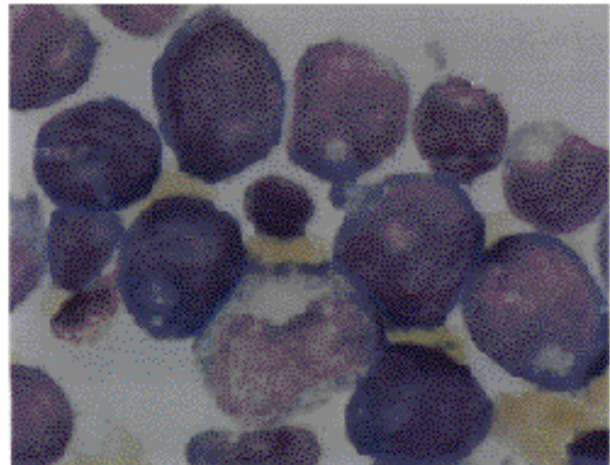
Primary extramedullary involvement was observed in 4 patients (numbers 1, 6, 9, and 12), of whom 3 showed central nervous system involvement. Patient 12 had a primary intracranial manifestation of the AML, manifesting with neurologic impairment (impairment of visus and occurrence of double pictures). Cranial computerized tomography showed an intracranial tumor, and histologic examination demonstrated myeloid blast cells.

Patient 9 suffered from a balanoposthitis that did not respond to antibiotics and ambulatory treatment. The histologic examination of tumor lesion showed blast cells as a first manifestation of AML.

Morphology

The bone marrow or peripheral blood smears of all patients showed blast cells of various size. The blasts were large with a variable nucleocytoplasmatic ratio and had a round or oval nucleus

A



B

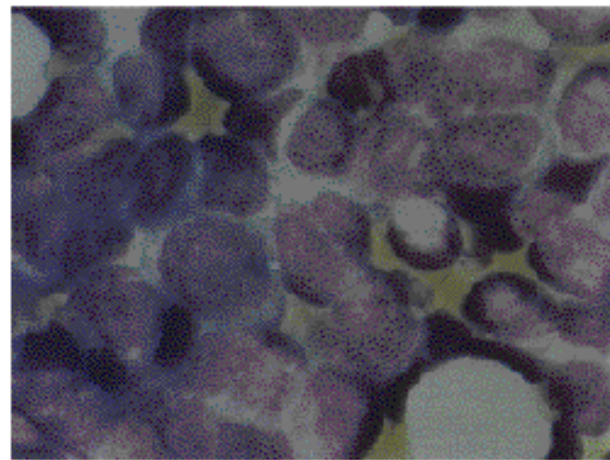


FIGURE 1. Morphologic features of myeloid/NK cell precursor acute leukemia. A: MG-stained bone marrow smears of patient 12. The leukemic cells show a variable nucleocytoplasmatic ratio with round or oval nucleus. B: Morphologic findings of patient 9 with AML-M3. The predominant cell is the highly abnormal promyelocyte. The cytoplasm is tightly packed with coarse red or purple granules.

and 1 or more nucleoli. The cytoplasm contained Auer rods. The blasts were positive for MPO (Figure 1A). Patient 9 had the typical morphology of AML-M3 with the predominant abnormal promyelocyte (Figure 1B). According to the FAB classification, 5 cases were M0 or M1 (numbers 4-8), 4 were myelomonocytic (M4) or monocytic (M5) (numbers 1, 3, 10, and 11), 1 (number 12) was AML-M2, and 1 (number 2) was myelodysplastic syndrome (MDS)/erythroblastic refractory anemia with blasts in transformation (RAEB-t) [17].

TABLE 3. Immunophenotyping Findings in Patients With Myeloid/NK Cell Precursor Acute Leukemia*

No.	CD7	CD13	CD33	CD38	CD56	HLA-DR	MPO
1	94.7	92.1	92.5	98.2	28.4	76.3	77.2
2	77.1	76.2	77.7	96.4	78.5	62.8	64.2
3	72.8	65.3	85.0	95.2	55.9	66.1	78.2
4	82.9	70.8	69.2	92.2	45.5	68.6	1.8
5	91.3	96.2	92.3	97.4	39.9	ND	1.4
6	18.6	19.0	95.4	97.5	92.3	11.2	92.7
7	99.1	62.0	97.6	99.4	18.1	37.5	95.6
8	75.9	53.2	43.6	93.2	51.7	48.0	46.0
9	87.2	69.4	69.5	91.2	71.3	25.6	58.9
10	96.2	24.6	90.2	97.8	94.0	94.6	92.2
11	52.4	72.9	83.7	92.5	41.4	32.0	9.0
12	76.4	65.9	78.4	66.9	64.0	33.5	33.2

*ND indicates not determined. Data are percentages of blast cells for each marker.

Immunophenotyping

The immunophenotypes of all 12 cases are listed in Table 3. All cases expressed the so-called NK cell antigen CD56 and the T-cell lymphoid-associated antigen CD7. It is well known that both antigens are not restricted to a special population of normal cells; thus, CD56 is found in several hematopoietic and neuronal cells. Similarly, CD7 is not specific for T cells. In addition, all patients expressed 2 of the typical myeloid antigens CD13/CD33/CD65 (Figure 2), and all were MPO⁺/LF⁻ as well. Cytoplasmatic CD79a and CD3 were negative, and all cases were negative for other B- or T-cell antigens (CD19, CD20, CD22, CD2, CD3, CD5).

Genotypic Analysis

The results are listed in Table 4. Southern blotting was done in 5 of the 12 patients. No clonal rearrangements of the TCR- β , - γ , or - δ chain genes or the Ig H and Ig κ gene were detected.

Cytogenetic Analysis

The results of cytogenetic examinations are listed in Table 5. Cytogenetic analysis was available in 10 of 12 patients (83.3%). Two of them have had a normal karyotype (numbers 4 and 6), and patient 9 with AML-M3 showed the typical genetic aberration t(15;17). All other patients had complex cytogenetic aberrations with trisome chromosomes and hyperloid or hypertetraploid metaphases.

Therapy and Clinical Course

Treatment protocols, clinical response, and overall survival (OS) are listed in Table 6. The majority of patients (10 patients) received aggressive induction chemotherapy consisting of Ara-C and anthracycline (100 mg/m² Ara-C for 24 hours on days 1-7, 45 mg/m² daunorubicine on days 3-5, for example, or 2 g/m² Ara-C on day 1, 3, 5, and 7; 12 mg/m² idarubicine on days 1-3). Two patients (numbers 6 and 8) received palliative chemotherapy (vepeside by mouth, for example, or subcutaneous Ara-C).

Patient 9, suffering from AML-M3, was treated with all-*trans*-retinoic acid (ATRA) and induction therapy. Two patients (numbers

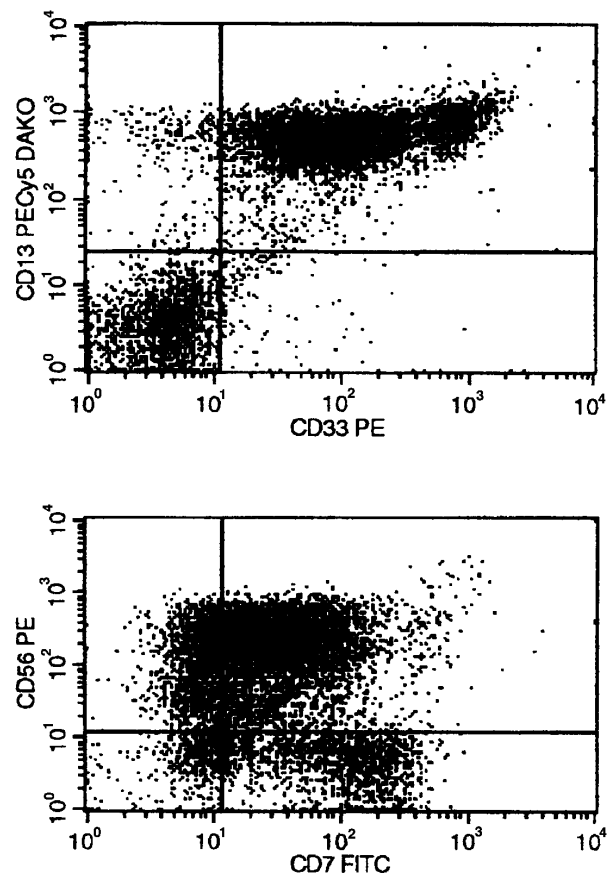


FIGURE 2. Typical flow cytometric analysis of CD13/CD33 and CD7/CD56 in patients with myeloid/NK cell precursor acute leukemia (patient 12).

9 and 12) received local radiation because of central nervous system manifestation. Five patients were successfully treated and achieved complete or partial remission (numbers 3, 4, 9, 11, and 12), whereas 7 patients were refractory to chemotherapy and had refractory disease. Median overall survival for this group was 4.5 months.

Three of the patients (numbers 3, 4, and 12) achieved complete or partial remission (CR or PR) but relapsed within 6 months, and

TABLE 4. Genotyping Findings in Patients With Myeloid/NK Cell Precursor Acute Leukemia Using Southern Blotting (5 of 12 Cases Examined)*

No.	IgH	Ig κ	TCR- β	TCR- γ	TCR- δ
1	G	G	G	G	G
7	G	G	G	G	G
9	G	G	G	G	G
10	G	G	G	G	G
11	G	G	G	G	G

*IgH indicates Ig heavy chain; G, germline; TCR, t-cell receptor.

TABLE 5. Cytogenetic Findings in Patients With Myeloid/NK Cell Precursor Acute Leukemia

1	45, XX
2	ND
3	45, XY, t(3;17)(q21; p13), -7, der(9)T(9:?) (q34;β)
4	46, XX
5	47, XY, +8, t(9;22)(q34;q11)
6	46, XX
7	47, XX, +8, t(9,11)(p22,q23)[10]/46, XX, del7(q32), t(9;11)(p22,q23)[2]
8	ND
9	46, XY, t(15,17)
10	46, XY, t(11,14)(11q,14q), t(9p,11)
11	46, XX, t(3,3)(q21;q26): inc[13], 46 XX: inc[1]
12	46, XX[2], hypoploide, hyperploide, hypertetraploide

all 3 of these patients died of leukemia or related complications within a short time. Patient 11 received allogeneic bone marrow transplantation from an HLA phenotypically identical sister and is in CR. Patient 9 committed suicide; he was in complete remission at that time. The disease-free survival of this group was 5.4 months.

DISCUSSION

In this study, 12 cases of AML were characterized by thorough investigation of morphologic, immunophenotypic, genotypic, and clinical features. All leukemic cells showed immature immunophenotypic appearance, with typical expression of 2 of the myeloid antigens CD13/CD33/CD65, and were MPO⁺/LF⁻ with coexpression of CD7/CD56.

The phenotype of NK cell progenitor cells is considered to be CD34⁺, CD33⁺, CD7⁺, CD2^{+/-}, CD56⁻, whereas mature NK cells are CD34⁻, CD33⁻, CD7⁻, CD2^{+/-}, CD56⁺. The presented cases were of different phenotypes from these.

One of the main clinical features of this series is the high incidence of extramedullary involvement of the myeloid/NK precursor AML (3 patients with central nervous system involvement and one with a balanoposthitis). These clinical, immunophenotypic, and genotypic findings showed that the immunologic myeloid/NK cell type of AML appears to be a distinct clinicopathologic entity.

Recently, Suzuki et al [10] described 7 cases of myeloid/NK precursor AML that were positive for CD7/CD33/CD34/CD56 and (frequently) HLA-DR. Leukemic cells showed no rearrangement in the TCR-β, -γ, or IgH genes. The authors concluded that the blasts might be phenotypically identical to those of myeloid/NK cell precursor phenotype. The incidence of extramedullary involvement was high, and the therapeutic response and therefore the clinical outcome were very limited. In this series, 5 patients showed clinical response to induction chemotherapy and achieved CR or PR. Nevertheless, median OS was very short (4.5 months).

In the present series, 5 patients had features of M0 or M1 according to FAB classification. AML-M0 is characterized by immature lymphoblastoid morphology, expression of myeloid anti-

TABLE 6. Therapeutic Response and Clinical Outcome in Patients With Myeloid/NK Cell Precursor Acute Leukemia*

No.	Age	Sex	FAB	Treatment	Survival Response	(Months)
1	39	F	M5a	Ara-C, idarubicine	PD	0
2	69	M	MDS-RAEB-t	Ara-C, daunorubicine	NC	6
3	60	M	M4	Ara-C, daunorubicine	PR	7
4	75	F	M1	Ara-C, daunorubicine	CR	12
5	30	M	M0	Ara-C, idarubicine	PD	0
6	73	F	M1	Ara-C	PD	0
7	59	F	M0	Ara-C, daunorubicine	PD	0
8	85	F	M0	vepeside oral	NC	7
9	47	M	M3	ATRA, Ara-C, idarubicine	CR	9
10	66	M	M5	Ara-C, daunorubicine	PD	1
11	39	F	M4	Ara-C, idarubicine	CR	5
12	53	F	M2	Ara-C, idarubicine	CR	8

*NC indicates no change; PD, progressive disease.

gens, lack of T- or B-cell antigens, complex karyotype, and poor prognosis. CD7 was found in ~40%; CD56 expression has not been described [18,19]. It is possible that some AML-M0 might be classifiable as myeloid/NK precursor acute leukemia, but further investigation is needed.

Extramedullary involvement of AML is a rare complication. Kurtzberg et al [20] described a population of CD7⁺, CD4⁻, CD8⁻ acute leukemias with high incidence of extramedullary involvement and poor prognosis, but unfortunately CD56 coexpression was not investigated. Suzuki et al [10] described 7 cases of CD7/CD56-positive myeloid/NK cell precursor AML, again, with high incidence of extramedullary involvement.

CD56 is a cell adhesion molecule, and therefore its expression on tumor cells is supposed to play an important role in extramedullary localization of AML. In a review, Byrd et al [21] described CD56 as a possible prognostic risk factor for extramedullary involvement, but other investigators did not confirm the findings [4,22].

In this report, 7 cases showed no clinical response to aggressive chemotherapy (Ara-C and anthracycline), and patients died within 7 months (median OS of 4.5 months). These results and the high incidence of extramedullary involvement support the clinicopathologic concept of a myeloid/NK cell precursor acute leukemia and the need for alternative therapeutic concepts.

Despite the fact that the leukemias reported seem to be very heterogeneous, one should be aware that CD56/CD7 positivity is assigned to be a biologic prognostic feature for the clinical course rather than a new morphologic entity according to the FAB classification.

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