

# Acute Megakaryoblastic Leukemia in Children: Diagnosis and Management Challenges in Resource-Poor Countries

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**Abstract:** Acute Megakaryoblastic Leukemia (AMKL) is a rare subtype of acute myeloid leukemia classified as AML M7 by the French–American–British (FAB) Leukemia Cooperative Study Group. We reviewed the records of children aged less than 18 years with AMKL during the period from January 2003 to December 2010. The diagnosis of AMKL was established on the basis of the FAB criteria and confirmed by immunophenotyping. Eight cases were assigned for this period. The incidence rate of AMKL was 5.5 % of AML. The median age at the time of diagnosis was 1 year. The karyotype presented translocation (1, 22) in two cases. One girl had Down syndrome (DS). Treatment included two inductions based on daunorubicin and cytosine arabinoside (7+3) followed by two consolidations with high dose of cytosine arabinoside (16 g/m<sup>2</sup>). Complete remission (CR) was achieved in 3 patients (43%). One patient underwent allogeneic stem cell transplant (SCT) and is still enjoying continuous CR 5 years after treatment. Other patients died from failure or relapse. In this small series from a single institution, reported incidence of AMKL is underestimated probably due to the difficulties of diagnosis. The prognosis was poor, particularly because of unavailability of intensified chemotherapy treatment and allogeneic SCT.

**Keywords:** Acute Megakaryoblastic Leukemia, children, treatment.

## INTRODUCTION

Acute Megakaryoblastic Leukemia (AMKL) has been classified as the seventh subtype of Acute Myeloid Leukemia AML (M7) by the French–American–British (FAB) Leukemia Cooperative Study Group [1]. AMKL has been identified as a separate entity for long time [2]. Although initially thought to be rare among children, AMKL has been diagnosed with increasing frequency in this age group [3]. It is the commonest form of AML in children with Down Syndrome (DS) [4, 5]. Most of the evidences regarding this entity originate from developed countries [3, 6-8], there is one case report from India [9]. Thus, we decided to evaluate our experience in diagnosis, management and outcome of children with AMKL.

## PATIENTS AND METHODS

### Patients and Diagnostic of AMKL

All children diagnosed with AMKL in the Department of Hematology and Pediatric Oncology, 20 Août 1953 Hospital in Casablanca, from January 2003 to December 2010 were included in the study.

Details of clinical presentation, laboratory findings at the time of diagnosis, therapy received, and outcome were collected from the case files and AML database.

Acute leukemia was diagnosed by the presence of at least 20% blasts in the bone marrow. The diagnosis of AMKL was established on the basis of the FAB criteria by studies of cell morphology and cytochemistry [1] and was confirmed by immunophenotyping [10].

Cytogenetic studies were performed on bone marrow samples taken at the time of diagnosis and analyzed by standard methods.

### Treatment

All children were included according to national AML protocol used since April 2003 (AML-MA 2003) which consists of a pre-phase based on Hydroxyurea at 50 mg/Kg/day during 4 days if WBC  $\geq$  50.000 G/L, two inductions courses (Daunorubicin at 50 mg/m<sup>2</sup>/day x 3 days and cytosine arabinoside at 200 mg/ m<sup>2</sup>/day x 7 days) with intrathecal therapy followed by two consolidations with 2g/ m<sup>2</sup> of cytosine arabinoside twice a day during 4 days with Asparaginase at 6000 IU/m<sup>2</sup>.

## RESULTS

During the study period, 145 patients under 18 years were diagnosed with AML and eight patients with AMKL. The incidence rate of AMKL was therefore 5.5 % of AML.

The median age at the time of diagnosis of AMKL was 1 year (range: 6 month 2 years). The M:F ratio was 2:6. The average time for consultation was 2 months (range: 2 weeks-1 year). The diagnosis was made based on the signs of medullar insufficiency in all cases. Presenting findings

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**Table 1. Clinical, hematological and one marrow findings at the time of diagnosis.**

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age (months)	18	9	24	12	6	6	8	20
Sex	F	F	M	M	F	F	F	F
Anemic syndrome	+	+	-	-	+	+	+	+
Infectious syndrome	-	+	+	+	+	+	+	+
Hemorrhagic syndrome	+	+	+	+	-	-	+	+
Splenomegaly	+	+	-	-	-	+	-	+
Hepatomegaly	-	+	-	-	-	-	-	-
Lymph nodes	-	+	-	-	-	+	-	+
Down's syndrome	+	-	-	-	-	-	-	-
Hb (g/dl)	5	6	12	13	8	11	4	3
WBC (x 10 <sup>9</sup> /l)	135	33	7	24	17	4	31	139
Circulating blasts (%)	84	80	34	60	40	0	31	90
Platelets (x 10 <sup>9</sup> G/l)	71	74	28	15	19	21	26	13
BM cellularity	+++	++	++++	+++	++++	+	++/-	++++
BM % blasts	96		45	75	94	65	94	90
Cytochemistry (MPO)	-	-	-	-	-	-	-	-
Cytogenetic study	Trisomy 21	T (1,22) -8,-19	49 XY +2,+8,+22	ND	Trisomy 22	T (1,22)	normal	T (16,18)

included bone pain in 1 patient and bilateral exophthalmos in 1 patient. One female had Down syndrome. Radiological exams found diffuse bone lysis in 1 case.

Table 1 summarizes clinical, hematological and bone marrow features at the time of diagnosis.

In all cases, bone marrow aspirate confirmed the diagnosis of AML M7 and leukemic cells expressed at least one platelet-associated antigen (CD36, CD41a, or CD 61). The karyotype objectified translocation (1, 22) in two cases (Table 1).

Parents refused treatment in one case. 7 patients received induction course. The patient with Down syndrome died at day 15 of chemotherapy from hemorrhagic syndrome despite platelet transfusion, she had thrombocytopenia at 3000/mm<sup>3</sup>. Three patients did not achieve complete remission (CR) after first cycle of chemotherapy and died in disease progression. All 3 remaining patients achieved CR (43%). One patient (case 3) underwent allogeneic stem cell transplant (SCT) in another country with genodentic donor and is still enjoying continuous CR 5 years after SCT; whereas other two patients died from relapse after 9 months and 3 years respectively and half died on completion of therapy.

Of whole AML cohort, 70% of patients achieved CR after induction courses. Among them, 27% attained CR and 36% experienced hematological relapse.

## DISCUSSION

In this small series from a single institution in Morocco, 5.5% of children with AML were identified as AMKL. The incidence of AMKL varies between 7.1 and 19.1% of AML cases in children [3, 6-8]. Recently, Hama *et al.* have reported much higher incidence of AMKL at 23.2% in Japan [11]. This may indicate that the reported incidence of AMKL in our series may be an underestimation probably due to the difficulties of diagnosis.

The median age at diagnosis was 1 year, which was lower than that in the total group of children with AML (13 years) and also lower than what is reported in literature [6, 8, 11].

With the available combination of morphologic, cytochemical, cytogenetic, and immunophenotypic methods, AMKL can be reliably diagnosed [12]. In all children, the expression of at least one megakaryoblastic antigen could be shown.

Acute megakaryoblastic leukemia is the most frequent type of AML in children with DS, and its prognosis is excellent in this group of patients with less intensive chemotherapy [4, 5, 11]. The remission rate is approximately 96% with overall and event-free survival (EFS) of 79% [11]. Unfortunately, death of the female with DS was due to the treatment toxicity. On the other hand, in children with

**Table 2. Bone marrow features.**

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
BM Morphology								
Cellularity	+++	++	++++	+++	++++	+	++/-	++++
% blasts	96		45	75	94	65	94	90
Cytochemistry								
MPO	-	-	-	-	-	-	-	-
Immunophenotype								
CD41a (%)	88	+	81	+	88	90	+	40
CD61 (%)	87	+	85	+	82	84	+	86
CD36 (%)	94	+	ND	ND	ND	ND	ND	2
Cytogenetics study	Trisomy 21	t(1,22) -8,-19	49 XY +2,+8,+22	ND	Trisomy 22	t(1,22)	normal	t(16,18)

non-DS, AMKL appeared to be more heterogeneous and showed close association with t(1;22)(p13;q13) [6, 8, 11, 13].

The outcome of children with non-DS was poor in previous report with 2 year overall survival (OS) in only 14% [6], but a recent study showed improvement of OS and EFS at 76 and 57% respectively [11]. Reinhardt *et al.* reported a significant improvement in the CR rate and in EFS in AMKL patients from early AML-BFM 87 trial (58%/11%) to AML-BFM 93 (77%/41%) and AML-BFM98 (84%/41%) after intensified induction treatment [8]. In this trial, AMKL was not identified with especially poor prognosis. While increased treatment intensity has improved outcomes for children with acute megakaryoblastic leukemia (AMKL), the prognostic and therapeutic implications of megakaryoblastic differentiation remain controversial with some groups treating such disease as high risk and recommending hematopoietic stem cell transplantation (HSCT) during first remission, while others treating it as standard risk in the absence of unfavorable cytogenetics and/or a poor response to induction therapy [14].

In this study, we report a poor outcome with CR rate at 43% and only one survivor at 5 year (14%). However, in patients with AMKL compared the total group of children with high risk AML (n=50) treated in AML-MA study, the CR rate was comparable at 47% and the 5-year OS was at 17%.

In conclusion, we have characterized the clinical and biologic features and outcome of a small series of pediatric patients with AMKL. Treatment included standard chemotherapy and prognosis was poor. This finding supports the new Moroccan AML design based on intensification of therapy with improvement in supportive care.

#### CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

#### ACKNOWLEDGEMENTS

We thank Dr Uma Athale for her critical review of this manuscript.

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Received: January 06, 2014

Revised: April 21, 2014

Accepted: May 02, 2014

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