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ORIGINAL ARTICLE

Outcome of Acute Myeloid Leukemia in Children Adolescents and Young Adults Treated with an Uniform Protocol in Casablanca, Morocco

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Abstract Treatment of acute myeloblastic leukemia in children, adolescents and young adults (AYA) is a challenge in low-income countries. To evaluate treatment outcomes of children ($\leq$ 15 years) and AYA (15–30 years) diagnosed with novo AML and treated in a single center according to the AML-MA 2011 protocol. From January 2011 to December 2015, eligible patients (age $\leq$ 30 years) with novo AML had been enrolled on a uniform treatment protocol. The diagnosis was confirmed according to the FAB classification using the WHO 2008 criteria. Patients with WBC $\geq$ 50 G/L had pretreated 4 days of hydroxyurea followed by two inductions and two consolidations. Supportive care consisted of transfusion of labile blood products, antibiotics and antifungals, and patient and family education by the hygiene team. 155 patients were recruited, 41 were $<$ 15 years old (22 boys, median age 7.8 years). Of the 114 AYA enrolled, (48 women, median age 23 years). Complete remission after two inductions was 28/41 (68.3%) of the children, including 100% of the children in the favorable group and 71/114 (62.3%) of the AYA, 22 of whom (68.7%) were in the favorable group. The number of deaths among children was 6 (14.6%). The evaluation of the AML-MA-2011 National Protocol in the age groups of children and AYA reveals that the objective of treatment is almost achieved in terms of complete remission in the two age groups.

Keywords Children · Adolescents and young adults · AML · Outcome protocol

Introduction

With improved risk assessment, therapeutic advances and supportive care, about 50% of newly diagnosed children, adolescents and young adults (AYA) diagnosed acute myeloid leukemia (AML) can be cured in high-income

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countries [1–6]. However, similar survival benefits are not seen in patients in low- and middle-income countries.

In Morocco, the main causes of poor response in the treatment of patients with AML are delayed diagnosis (before treatment), death during induction, failure of induction and discontinuation of treatment [7]. In 2011, the AML-MA-2011 national protocol was adopted to treat AML patients according to international standards and focused on improving care supports, in particular, infection prevention and management, Transfusion support, the implementation of hand hygiene, and education of patients, families and nurses. The objectives of the AML-MA-2011 protocol were to obtain more than 70% complete remission rate in the favorable group, less than 10% on treatment-related mortality and 4-year event-free survival (EFS) of 40%.

Aim of this Study

To evaluate treatment outcomes (total remission rate, overall survival [OS] and EFS) of children ($\leq$ 15 years) and AYA (15–30 years) diagnosed with de novo AML and treated in A single center according to the AML-MA 2011 protocol.

Patients and Methods

From January 2011 to December 2015, eligible patients (age $\leq$ 30 years) with de novo AML were enrolled on a uniform treatment protocol. Patients with secondary AML, Down syndrome, acute promyelocytic leukemia were excluded.

The diagnosis was confirmed according to the FAB classification using the WHO 2008 criteria. At the time of diagnosis, myeloperoxidase and immunophenotyping were performed.

The conventional cytogenetic study was performed in RGH band on medullary sampling. Patients with leukocytosis (WBC $\geq$ 50 G/L) had pretreated 4 days of hydroxyurea at 50 mg/kg/day followed by 2 inductions and 3 consolidations. The two inductions were cytarabine (100 mg/m^2/12 h for 10 days), daunorubicin (50 mg/m^2 on days 2, 4, 6 for the first induction and days 1, 3, 5 for the second) and etoposide 100 mg/m^2 for 5 days for the second induction). The first two Consolidations consisted of cytarabine (3 g/m^2/12 h days 1–3 for first and second consolidation) plus daunorubicin (30 mg/m^2 on days 3, 4 on first consolidation). L-asparaginase 6000 UI/m^2 on day 4 was given at the second consolidation. The third consolidation consisted cytarabine (1 g/m^2/12 h days 1–3) and daunorubicin (30 mg/m^2 days 1–3). All patients had received central nervous system prophylaxis. Patients with neurological impairment received additional intrathecal injections.

Supportive care is made up of transfusions of labile blood products, antibiotics, antifungals, and patient and family education by the hygiene team.

Complete remission (CR) was defined as a normal clinical examination without chloromas, with blood count (NFS): neutrophils $\geq$ 1.0 G/L, platelets $\geq$ 75 G/L without transfusion and at the end Of induction II the myelogram showed normal haematopoietic elements and $<$ 5% of blasts.

The data had been collected from medical records. Data processing was performed using SPSS version 18.0 and Excel 2007. The Kaplan–Meier method was used to determine the different survivals. The Pearson Chi square test had been used to compare proportions. The threshold of significance of the differences corresponds to the alpha risk less than or equal to 5%.

Throughout the work, ethical considerations had been taken into account. The data remained confidential. The study had no negative impact on patients.

Results

During the study period, a total of 155 patients were recruited, 41 were $<$ 15 years old (22 boys, median age 7.8 years). Among the 114 AYA enrolled, 48 were women and the median age was 23 years. In children, median hemoglobin was 6.75 g/dl and platelets 39.5 G/L, 15/41 (36.6%) had FAB AML2 and 36/41 (87.8%) had Immunophenotyping. In the AYA 32 (28.1%) were hyperleukocytosis, 7.38 g/dl and 52.81 G/L were respectively median hemoglobin and platelets rate, 31/114 (29.8%) had AML1 and 89/114 (78.1%) had immunophenotyping. Cytogenetics was performed in 37 (90.2%) children of whom 10 (27%) had a favorable group, 22 (59.5%) were intermediate and 5 (13.5%) were unfavorable. 109 (95.6%) of AJA performed the karyotype: 32 (29.4) were favorable, 60 (55%) were intermediate, and 17 (15.6%) were unfavorable groups (Table 1). The median time between diagnosis and treatment was 11.5 days for children and 29.9 days for AYA. Complete remission after two inductions was 28/41 (68.3%) of the children, including 100% of the children in the favorable group and 71/114 (62.3%) of the AYA, including 22 (68.7%). The failure rate was 21 in the two age groups, of which 4 (9.8%) were children and 17 (14.9%) were among AYA. The number of deaths in children is 6 (14.6%), of which 3 occurred during the first 15 days of induction and the rest from the 15th to 42nd day. Among AJA, 22 (19.3%) deaths had been recorded including 5 in the first 15 days and 17

from the 15th to the 17th day. Causes of death were infections: 3 cases in children and 10 in AJA, haemorrhage: 2 cases in children and 10 in AYA and leukostasis: 1 case in children and 2 in AYA.

In the children's group, overall survival at 4 years was 41.9%, of which 60% was in the favorable prognosis group, 35.4% in the intermediate group and 40% in the unfavorable group (Fig. 1). The 4-year survival rate was 29.5%, of which 60% was in the favorable group, 34% in the intermediate group and 20% in the unfavorable group (Fig. 2).

Among the AJAs, the cumulative OS at 4 years was 41.9%, of which 42.2% was favorable, 50.5% in the intermediate group and 29.8% in the unfavorable group (Fig. 3). The cumulative EFS at 4 years is 25.1%, of which 24.9% were in the favorable group, 26.9% in the intermediate group and 17.6% in the unfavorable group (Fig. 4).

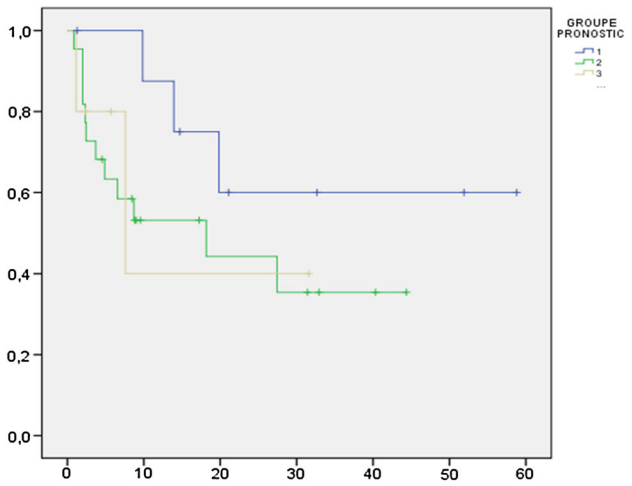

Fig. 1 OS by prognostic group (children). 1-Favorable; 2-intermediate, 3-unfavorable

Discussion

The National Treatment Protocol for AML has been adopted in 2011 to treat all patients younger than 60 years of age, including children and AYA, with emphasis on supportive care, including infection prevention and management, support Transfusion, the implementation of hand hygiene, and education of patients, families and nurses.

The children median age at diagnosis of 7.8 years found in children in our study is higher than that reported in 2016 by Jastaniah et al. [8] in the multicenter SAPHOS Leukemia Group Study on the clinical and therapeutic characteristics of children with AML Novo which is 5.5 years. It is as high as the 6.9 years reported by Canner et al. [9] of the American pediatric oncology group. The sex ratio in the two age groups are close and superimposable at 1.2 found in Jas hyperleucocytosis taniah Jastaniah et al. [8]. About one-third of patients in both age groups were hyperleucocytosis at diagnosis, which is consistent with SAPHOS results in 2016 [8].

Analysis of the distribution of FAB subtypes showed a predominance of AML2 (36.6%) followed by subtype

Table 1 Characteristics of children, adolescents and young adults treated with the 2011 AML-MA protocol

	All patients N = 155	Groupe 1 Age ≤ 15 years n = 41	Groupe 2 15 years > Age ≤ 30 years n = 114
Median age (years)	19	7.8	23
Sex ratio H/F	1.3	1.2	1.4
Hyperleukocytosis ≥ 50 G/L	44 (28.4%)	12 (29.3%)	32 (28.1%)
FAB M0/M1/M2/M4/M5/other	7/39/47/18/16/28	3/5/15/3/5/10	4/34/32/15/11/18
Immunophenotype (yes/no)	125 (80.7%)	36 (87.8%)	89 (78.1%)
Cytogenetics	146 (94.2%)	37 (90.2%)	109 (95.6%)
t (8; 21)	28 (19.17%)	9 (24.3%)	19 (17.4%)
Inv 16 or t (16; 16)	14 (9.6%)	1 (2.7%)	13 (11.4%)
Normal karyotype	52 (35.6%)	15 (40.5%)	37 (32.5%)
Complex karyotype	10 (6.8%)	2 (5.4%)	8 (7%)
11q23 abnormalities	5 (5.4%)	1 (2.7%	4 (3.5%)
Del/loss chromos 5 or 7	3 (2.2%)	2 (5.4%)	1 (0.9%)
Other	34 (23.3%)	7 (18.9%)	27 (23.7%)
Pronostic groupe			
Favorable	42 (28.8%)	10 (27%)	32 (29.4%)
Intermediate	82 (56.2%)	22 (59.5%)	60 (55.1%)
Unfavorable	22 (15%)	5 (13.5%)	17 (16.4%)

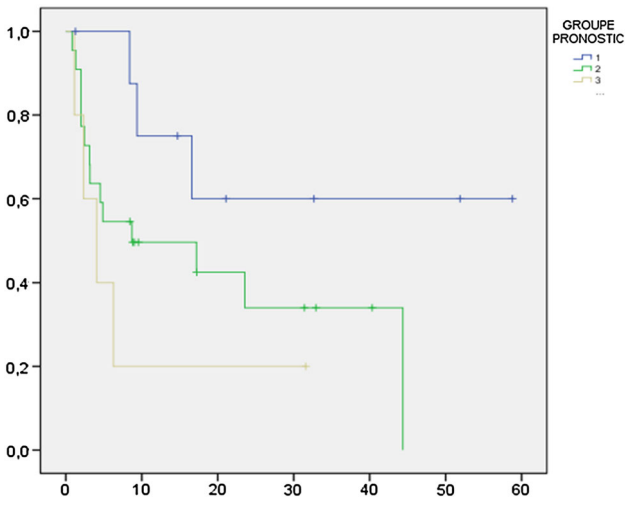

Fig. 2 EFS by prognostic group (children). 1-Favorable; 2-intermediate, 3-unfavorable

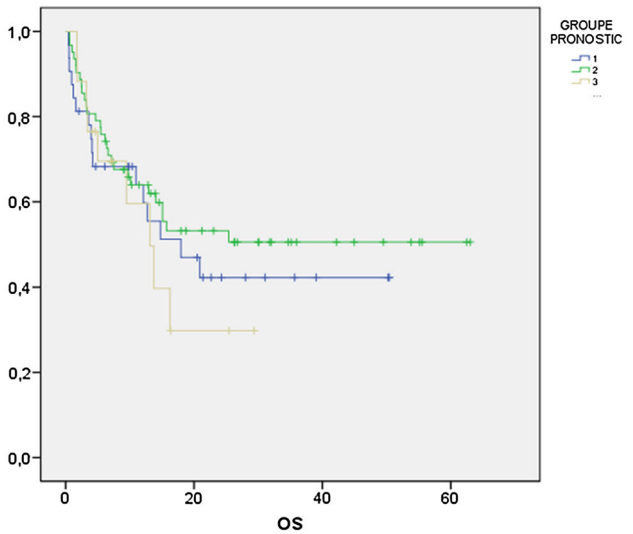

Fig. 3 OS by prognostic group (AYA). 1-Favorable; 2-intermediate, 3-unfavorable

AML5 (12.2%) in the children groupe. This result is different at the frequency of M2 (27%) and M5 (22%) subtypes in the Berlin-Frankfurt-Münster group study in Germany [10], M2 (23%) and M5 (21%) reported in the MRC AML12 study in the United Kingdom [11] and the 30% M2 and 18% M5 in the AML99 study of the Japanese AML study [12]. However, among the AYA, the distribution of FAB subtypes was dominated by M1 (29.8%), M2 (28.1%) and M5 (9.6%). This result is close to that reported by the American group of pediatric oncology in 2013 M2 (32.5%), M5 (10.8%) and M1 (19.9%) [9]. The differences in proportions observed, compared to other studies is certainly due to the size of our sample.

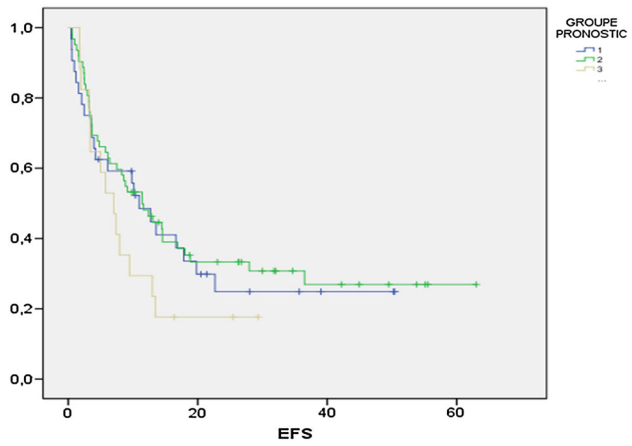

Fig. 4 EFS by prognostic group (AYA). 1-Favorable; 2-intermediate, 3-unfavorable

The number of patients with an abnormal karyotype is 59.5% in children and 67.5% in AYA less than the 70%–80% reported by several leukemia study groups [13, 14]. Molecular biology in patients with normal karyotype has become routine since November 2015. The t (8, 21) and inv 16 are respectively in children 24.3% and 2.7% and in AJA 17.4% and 11, 4% versus t (8; 21) 12%–15% and inv 8%–10%. The intermediate prognostic group is dominant in both age groups 59.5% in children and 55.1% in AYA, the favorable group is 27% in children and 29.4% in AJA and the unfavorable group is 13.5% (Children) and 16.4% (AYA). This result is similar to that reported by the COG study group AAML053: 24.1% (favorable group), 59.4% (intermediate group) and 16.5% (unfavorable group) [15].

Complete remission in children in ours study (68.3%) is lower than the proportions reported by several groups of studies between 80% and 95% [14, 16, 17]. It is 100% in the favorable group beyond the more than 70% set in goal. It is 62.3% among AYA less than 72.3% found in December 2007 by Creutzig U et al. in the study "Significance of age in acute myeloid leukemia patients younger than 30 years" [17]. In the favorable group it is 68, 7% lower than that of children and close to the goal. In the intermediate group, the proportions of complete remission are close to 70% in the two age groups, whereas in the unfavorable group it is greater in AYA than in children. The rate of death in the favorable group is 0% among children meeting the set goal of less than 10% and comparable to international standards [18–20] and 21.9% among AJAs greater than the target.

Overall and no-event survival at 4 years was 41.9% and 25.1%, respectively, than the results of several study groups [5, 18–20]. Overall survival in the favorable group in children is 60% better than in AYA which is 42.2%. The survival without event is 60% in children above 40% set as target by cons in AYA is 24.9%.

In summary, the evaluation of the AML-MA-2011 National Protocol in the child and AYA age groups reveals that the objective of treatment is almost achieved in terms of complete remission in the two age groups. The objective in terms of mortality during inductions and survival without event in the favorable group is reached in children and is not in AYA.

Conclusion

The evaluation of the AML-MA-2011 National Protocol in the age groups for children and AYA reveals that in children the goal has been achieved and there is still a lot of effort in AYA. It is therefore necessary to reinforce the achievements and consolidate them.

Compliance with Ethical Standards

Conflict of interest The authors do not declare any conflict of interest

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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