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Acute myeloid leukemia in childhood: fifteen-year experience in a single institution

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Abstract

Objective: To investigate the survival of children with acute myeloid leukemia (AML) before and after the introduction of a Berlin-Frankfurt-Munich-83 based protocol. To analyze the prognostic impact of age, gender, nutritional status, initial white blood cell count and use of etoposide in the remission induction phase.

Methods: This partly prospective/retrospective study comprised 83 children with AML diagnosed at Hospital das Clínicas, Universidade Federal de Minas Gerais, Brazil, between 1986 and 2000. Before 1991, 15 children were treated with 2-3 pulses of cytarabin plus daunomycin, followed by several consolidation/ maintenance schemes. From January 1991 to November 1992 a pilot study (n = 15) was carried out to test etoposide toxicity in the induction phase. Etoposide was randomized from December 1992 to June 1999.

Results: Median follow-up period was 5 years. Initial remission rates were 40 and 66% before or after the introduction of the German protocol, respectively (p = 0.11). Induction failure was largely due to death caused by infection and/or hemorrhage. The 5-year estimated probabilities of survival and of continuous complete remission were 31±5.4% and 49.7±7.4%, respectively. All 22 relapses involved the bone marrow. Age below 6 years at diagnosis was significantly associated with a poor prognosis. Sex, initial leukocyte count, and nutritional variables were not significant prognostic factors. The randomized addition of etoposide in the induction phase unexpectedly decreased the probability of complete remission at 5 years.

Conclusions: The introduction of a German-based protocol in 1991 significantly improved survival and duration of first remission. No plausible explanation for the unfavorable effect of etoposide was found.

J Pediatr (Rio J). 2003;79(6):489-96: Leukemia, myelocytic, acute/therapy/mortality, etoposide, child.

Introduction

The most common type of neoplasm during childhood is leukemia, accounting for around 30% of malignancies in patients less than 14 years old. Acute myeloid leukemia (AML) correlates to 20% of acute childhood leukemia. Limited progress has been made towards curing AML in recent decades, in contrast with the lymphoblastic form.[1,2]

Chemotherapeutic treatment of AML involves, succinctly, a phase during which remission is induced, followed by consolidation of remission and then by a maintenance chemotherapy phase, which some authors, differing from the consensus that exists on lymphoblastic leukemia, consider unnecessary.[2,3] The remission induction phase has the objectives of rendering the child asymptomatic and of reducing the percentage of myeloid, normal or

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neoplastic blasts, to less than 5% of the total number of cells with nuclei obtained from bone marrow samples.

Bone marrow transplantation is reserved for AML cases that relapse or those that are known to have worse prognosis, generally defined by cytogenetics at diagnosis or by confirmation of a minimum level of residual disease, detected by immunological or molecular biological methods during patient follow-up.[2]

Acute myeloid leukemia in children is a disease which has been little studied; in our country particularly so. To date there is little data on the disease or the survival of children affected by it in Brazil.[4-6] The majority of published articles refer to studies of adults.[7-11]

The present study takes as its objectives: to investigate the prognosis of children with AML diagnosed between 1986 and 2000 at the HC/UFMG, to compare survival curves before and after the adoption of the Minas Gerais Childhood Acute Myeloid Leukemia Treatment Group (GMTLMAI - *Grupo Mineiro para Tratamento de Leucemia Mielóide Aguda na Infância*) treatment protocol, and to evaluate the influence of prognostic factors such as age, gender, initial leukocyte analysis, nutritional status and randomized etoposide administration (VP-16) during induction chemotherapy.

Patients and methods

The population studied was made up of children younger than 16 years with an AML diagnosis made at the HC/UFMG during the period between 1986 and 2000.

The study was retrospective up to January 1991, and prospective from then onwards. The following data was collected: age, gender, weight and stature at diagnosis, initial leukocyte analysis, medullary blast morphology (FAB classification),[12] type of treatment received, global survival, event-free survival and complete clinical remission periods. The diagnoses of AML were made by a number of different hematologists depending upon when each child was admitted.

Since 1986 three different treatment systems have been used at the HC/UFMG: 1) until December 1990 (Group I, 15 children), remission was induced with cytarabine (100 to 200 mg/m²/day) from day one to seven and daunorrubicin (20 to 50 mg/m²/day) from the fifth to the seventh day. Two or three cycles were employed with intervals of approximately 30 days. Consolidation and maintenance phases were varied as there was no fixed protocol to follow: consolidation with high doses of cytarabine (ARA-C), followed, or not, by non-uniform maintenance phases (6-mercaptopurine with ARA-C; VP-16 and cyclophosphamide, for example); 2) in January 1991, the GMTLMAI protocol was started, based on the German 1983 protocol developed by the Berlin-Frankfurt-Munich (BFM) cooperative.[13] During this pilot phase all 15 patients received VP-16 (Group II); 3) from December 1992 onwards, the same protocol was used with another 53 children (Group III), but with the use or not of VP-16 during the induction phase being randomized. Patients with a morphological diagnosis of acute promyelocytic leukemia (n = 18) were excluded from the randomization and did not receive VP-16; those who presented with leukocyte counts below 5,000/mm³ at diagnosis received trans-retinoic acid at a dosage of 40 mg/m²/day for up to 30 days From June 1999 onwards, randomization was suspended since a preliminary analysis showed that survival was lower among patients who received VP-16.[14]

The treatment scheme based on the BFM-83 protocol (Table 1) consists of a pre-phase (employed for patients with leukocyte counts above 100,000/mm³ or considerable organ enlargement) and three phases (induction of remission; consolidation phases 1 and 2; maintenance). Maintenance is extended until two years after the start of the remission induction phase.

All of the children received prophylaxis against infections by *Pneumocystis carinii* with trimethoprim-sulfamethoxazole at a dosage of 5 to mg/kg/day of trimethoprim, divided into two doses three times a week.

The randomization of VP-16 was performed by drawing lots, at the point when the child was enrolled on the trial. This randomization was performed until June 1999, when it was suspended, as mentioned above. The total number of children submitted to randomization was 32. One family refused to allow their child to be randomized. Another child, although randomly selected to receive VP-16, did not do so due to an allergic reaction during the first infusion of the drug. In the analysis this child was considered to belong to the group with VP-16.

All patients were informed about the treatment, its procedures and risks. A Free and Informed Consent form was obtained for patients who continued to be treated at the Hematology Department of the HC/UFMG.

The *National Center for Health Statistics* growth curves were used as a reference for weight and stature Z scores.[15] The chi-square test was employed to verify associations between nominal variables. The ***t*** test was used in order to test differences between averages when variables were continuous and had normal distribution. When distribution was not normal, the Mann-Whitney test was used. The Cox model was used to analyze survival dependent upon continuous variables.[16] The Kaplan-Meier method was used to estimate global survival (time between diagnosis and death), event-free survival (EFS, time passed between diagnosis and an absence of remission, a relapse or death while in remission) and the duration of complete clinical remission (time between medullary remission and relapse or death while in remission).[17] The log rank test was used to compare curves.[18] One child, who abandoned treatment during the induction phase with no evidence of remission, was considered to have died when survival curves were

Table 1 - Treatment scheme applied in 68 children with acute myeloid leukemia, diagnosed at the Hospital das Clínicas of UFMG (GMTLMAI protocol, 1991-2000)

Pre-phase		
Drugs	**Dose and administration route**	**Administration days**
Arabinosil-citosine	40 mg/m², one dose/day- intravenous	Up to 7 days
Tioguanine	30 mg/m²/day - oral	Up to 7 days
Induction		
Drugs	**Dose and administration route**	**Administration days**
Arabinosil-cytoxin	100 mg/m²/day - intravenous, continuos	1 - 3
Arabinosil-cytoxin	100 mg/m²/dose 12/12h intravenous	3 - 8
Daunorrubicin	60 mg/m²/dose - intravenous	3 - 5
Etoposide (randomized)	150 mg/m²/dose - intravenous	6 - 8
Triple chemotherapy	intrathecal	1 (then, every 4 weeks)
Consolidation		
Drugs	**Dose and administration route**	**Administration days**
Phase 1		
Prednisone	40 mg/m²/dia - oral	1 - 28
Tioguanine	60 mg/m²/dia - oral	1 - 28
Vincristine	1,5 mg/m²/dose - intravenous	1, 8, 15, 22
Adriamycin	30 mg/m²/dose - intravenous	1, 8, 15, 22
Arabinosil-cytoxin	75 mg/m²/dose - intravenous	1 - 4, 8 - 11, 15 - 18, 22 - 25
Triple chemotherapy	Intrathecal	every 4 weeks
Phase 2		
Tioguanine	60 mg/m²/day - oral	29 - 56
Arabinosil-cytoxin	75 mg/m²/dose - intravenous	31 - 34, 38 - 41, 45 - 48, 52 - 55
Cyclophosphamide	500 mg/m²/dose - intravenous	29, 56
Triple chemotherapy	Intrathecal	
CNS radiotherapy	Administered after one year maintainance	every 4 weeks
Maintainance		
Drugs	**Dose and administration route**	**Administration days**
Tioguanine	40 mg/m²/dia - oral	1 - 28
Arabinosil-cytoxin	40 mg/m²/dose - subcutaneous	1 - 4 (every 4 weeks)
Adriamycin (ADR)	25 mg/m²/dose - intravenous	4 doses every 8 weeks
Triple chemotherapy	Intrathecal	every 8 weeks

analyzed. Two children who abandoned treatment, one during consolidation and the other after the suspension of chemotherapy, were considered to be alive up to the date of their last appointments. For all statistical tests the level of significance was set at p = 0.05 (two-tailed) for alpha error.

Results

Between 1986 and 2000, 122 children and adolescents with an initial diagnosis of AML were admitted for treatment to the HC/UFMG. Of these, 39 were excluded from the analysis for the following reasons: previous chemotherapy (21), treatment with a protocol designed for adults and performed at the Internal Medicine Specialist (11), previous diagnosis of myelodysplasia (three), death before start of treatment (two), AML later reclassified as ALL (two). Eighty-three patients, therefore, remained. Of these, 46 (55.4%) were male and 37 (44.6%) female. Three children abandoned the treatment (3.6%). For children who were alive on the cut-off date for the analysis (24/10/2002), the minimum follow-up was 37 days and the maximum 13 years

(median of five years). Of those that had died, minimum survival was four days and maximum ten years (median of 3.6 months).

The median of age at diagnosis was 7.4 years (8 months to 15.8 years); 16 of the patients (19.3%) were adolescents (older than 12). The median for global leukocyte count at diagnosis was 23,300 leukocytes/mm³, distributed as follows: 26 patients (32%) below 10,000; 28 (34%), between 10,000 and 50,000; 16 (19.5%) between 50,000 and 100,000; 12 (14.5%), above 100,000.

Only one child had their weight recorded on diagnosis. The average Z score (standard deviation from average for age) was -0.79±1.12, with a 95% confidence interval of -0.55 to -1.03. The probability that the average obtained would be equal to the reference population (average = 0 and standard deviation = 1) is $p = 1 \times 10^{-8}$. Five children did not have their stature recorded at diagnosis. The average of the Z scores was -0.66±1.16, with a 95% confidence interval from -0.91 to -0.40. The probability that the average obtained would be equal to the reference population is $p = 2 \times 10^{-6}$.

Standardized malnutrition prevalence, according to the Mora method, calculated from weight and stature at diagnosis, were 29.4% and 24.6%, respectively.[19]

The distribution of the children according to medullary blast morphology on diagnosis, according to the original myelogram report, was: M0, two children (2%); M1, 11 (13%); M2, 29 (35%); M3, 18 (22%); M4, eight (10%); M5, six (7%) and M6, four (5%) children. Five patients had no mention of classification on the original report and available laboratory slides were not sufficient for a reliable re-analysis of morphological sub-type.

Table 2 summarizes the general progress of the 83 children. The level of complete remission was 61.5%. For children treated before December 1990 (Group I), this was 40%; for children on the pilot phase of the GMTLMAI protocol (Group II) it was 73%, and in Group III (GMTLMAI trial phase) complete remission was achieved in 64% of cases. Children treated with the GMTLMAI protocol (pilot + trial) had higher levels of remission than those treated up to 1990, although without statistical significance (p = 0.11).

At the time of analysis, 56 of the 83 children had died. There were 24 deaths during induction (12 from infection, eight from infection associated with hemorrhage and four from hemorrhage). During consolidation there were three deaths (two from infection and one from infection associated with hemorrhage). Three children died while in medullary remission (two from infection and one from infection associated with hemorrhage). Four children died because the disease was resistant to induction chemotherapy. The remaining 22 deaths were the result of relapses of the disease. This happened during chemotherapy in two cases and after completing the planned 2 years of treatment in four cases. Relapse was in the bone marrow in 21 children and in one case it occurred simultaneously in the bone marrow and the central nervous system.

Two patients received allogeneic bone marrow transplantation: one, a girl, when the disease relapsed, after having completed chemotherapy as planned, died from acute complications due to the procedure; a boy is still alive two years after the transplantation which was indicated when he achieved remission after prolonged chemotherapy. Another boy, who received an autologous transplantation, died 8 months after the procedure, in medullary relapse. Of the 83 children included in the trial, only 34 were diagnosed after the Transplantation Unit at HC/UFMG was opened.

After five years' follow-up estimated probability of global survival, of complete remission and of event-free survival were 31.1%±5.4%, 49.6%±7.4%, and 30.5%±5.3%, respectively (Figure 1).

Table 2 - General evolution of the 83 children included in the GMTLMAI study according to the treatment groups

	Group I*	Group II*	Group III*	Total
Children included in the present study	15	15	53	83
Children with complete remission	6	11	34	51
Children submitted to chemotherapy	2	3	24	29
Deaths in the induction/consolidation	7	4	16	27
Dropouts in the indução/consolidation	1	0	1	2
Deaths in the maintainance phase (during remission)	0	0	3	3
Deaths after remission	5	6	11	22
Alive without remission	1	2	21	24
No follow-up after the end of the treatment	0	1	0	1

* Group I (1986 to 1990): before the GMTLMAI protocol; Group II (January to December 1991): pilot phase of the GMTLMAI protocol; Group III (1992 to 2000): GMTLMAI study.

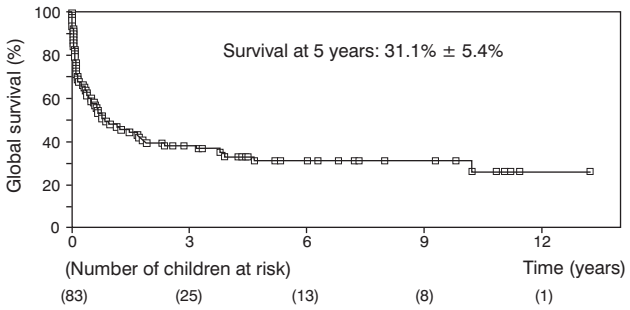

Figure 1 - Global survival curve of 83 children with acute myeloid leukemia according to the Kaplan-Meier method

The continuous Cox model revealed a tendency to increased survival with greater age. In the dichotomous model, the point of greatest discrimination for prognosis of probability of survival was at 6 years. For children younger than 6 years old 5-year survival was 23.9%±7.5% and above 6 years it was 35%±7.5% (p = 0.05). Gender did not significantly affect global survival (p = 0.96), nor complete clinical remission (p = 0.83). Initial leukocyte analysis was not a significant predictor for risk of death or relapse. No cut-off point between 10,000 and 100,000/mm³ was found to be significant to the comparison of survival curves.

Estimated 5-year survival was 31.7% for children with z scores for weight < -1.28 and 31.4% for those with z scores > -1.28 (p = 0.99). Using the same cut-off point for the stature z scores also revealed no influence on survival (p = 0.63). Curves for duration of complete clinical remission by weight and stature were also non-significant (p = 0.75 and p = 0.5, respectively).

Differences in survival between the children with promyelocytic leukemia (AML-M3; n = 18) and the remainder were also not significant (p = 0.93).

The estimated 5-year survival probability for the group treated between 1986 and 1990 (Group I) was 6.7%, for Group II 32%, and 39.4% for group III (p = 0.02). The probability of complete clinical remission at five years was 16.7% for the first group, 36.3% for Group II, and 61.2% for group III (p = 0.05). When the treatments were grouped into two categories, the global probability of survival at five years was 6.7% for Group I, and 37.3% for Groups II + III (p = 0.005; Figure 2).

Of the 68 children treated with the GMTLMAI protocol (Groups II e III), including randomized and non-randomized cases, 31 received etoposide and 37 did not. Global 5-year survival probability was 25.4%±7.9% for children who received etoposide and 48.7%±8.7% for the group that did not (p = 0.16). The probability of maintaining remission to five years was 33.3%±10.3% and 75%±10%, respectively (p = 0.006). The group of children who received VP-16 was compared with the group that did not, relative to the variables age at diagnosis and initial leukocyte analysis. Medians for age were 7.1 and 4.4 years, respectively, which is not a statistically significant difference (p = 0.76). Medians for leukocyte counts were 56,800/mm³ and 18,200/mm³, with differences in value distribution not being significant (p = 0.27).

Taking just the 32 randomized patients, Figure 3 illustrates survival curves (n = 32) and duration of clinical remission (n = 21). Both curves reveal worse prognosis for children who received etoposide, but only that for clinical remission shows a statistically significant difference (p = 0.11 and p = 0.04, respectively). The median for bone marrow recovery after induction (time between first day of chemotherapy and start of consolidation phase) was 28.5 days for the group that randomly received etoposide and 33 days for the group that did not, which difference lacks statistical significance (p = 0.32).

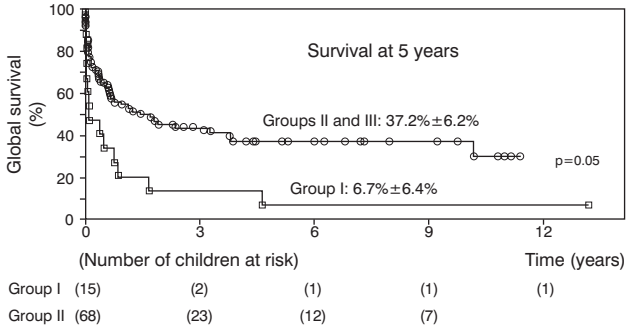

Figure 2 - Global survival curves, calculated by the Kaplan-Meier method, according to the groups of 83 children with acute myeloid leukemia. Group I (1986 to 1990): before GMTLMAI protocol; Group II (January to December 1991): pilot phase of the GMTLMAI study; Group III (1992 to 2000): GMTLMAI study

Discussion

The distribution of the disease by age groups was uniform, in common with data in international literature.[20-22] The discrete male predominance is reported in the majority of patient samples.[23]

Distribution of initial leukocyte analyses was similar to that found by the BFM-83 and 87 trials.[13] The frequency of morphological subtypes and their use as prognostic factors were not considered to be of value because the classification had been performed by a number of different professionals over the years and morphological revision, which would have provided more homogeneous criteria, was severely prejudiced because a large number of diagnosis slides were in poor condition in terms of coloration.

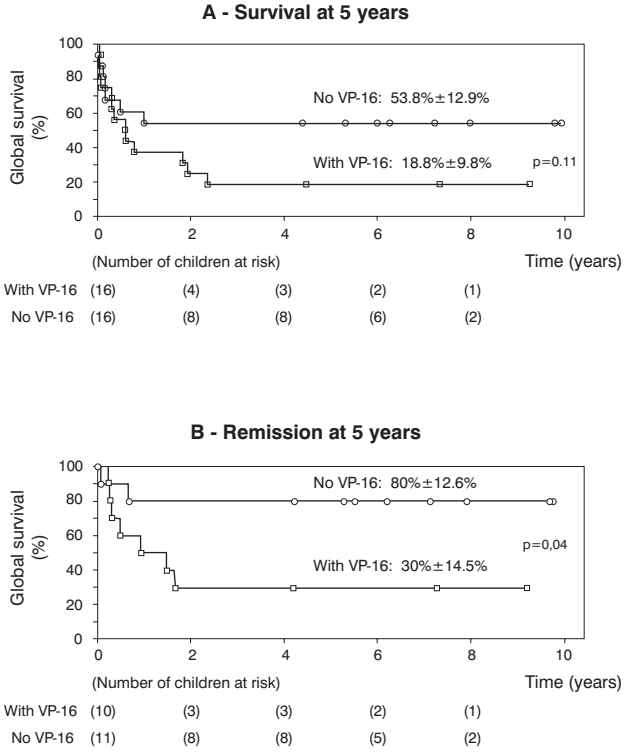

Figure 3 - Global survival curves (n = 31) and duration curves of complete clinical remission (n = 21), calculated by the Kaplan-Meier method, in children with acute myeloid leukemia, according to the administration of etoposide during the phase of remission induction (GMTLMAI protocol). Only the group submitted to the planned randomization was included (1992-1999)

The results of this patient sample reveal a higher rate of remission for Groups II and III when compared with Group I, treated before 1991. Among these, death during induction was the primary cause of failure to achieve remission. The difference in remission rates is probably due to increasing experience within the group over the years and improved use of antimicrobials and transfusions.

The results of these patients are similar to those obtained in certain developed countries. The Pediatric Oncology Group reported an estimated probability of EFS of 32.7%±2.2% at four years (n = 560).[24] The Argentinean Group of Acute Leukemia Treatment obtained a remission rate of 74% and an EFS of 37%.[22] Compared with the results reported by the BFM-83[13] group (remission 80%; six-year EFS 49%) or the British trial AML-10[25] (remission 92%; seven-year EFS 48%), the inferior results of the present study are primarily due to the lower remission rate and the elevated number of deaths during induction (24/83), factors that are most marked in Group I, made up of children treated before 1991.

The most frequent location of relapse was the bone marrow, agreeing with all series in the extant literature (74%[26] and 81%.[27] In terms of deaths during remission, the 6% in the present trial are similar to the British data from MRC-10 (9%) and BFM-83 (4%), with the most common cause of death being severe infection.[13,25]

Younger ages were also unfavorable prognosis factors, as in published literature.[28] Gender was not significant in the current patient sample, in common with some reports,[29] but in contrast with others.[24]

Initial leukocyte analysis may be considered a parameter for estimating the magnitude of leukemia at diagnosis. In the current sample this variable did not exercise any significant prognostic influence, even when a cut-off point of 10,000 leukocytes/mm³, which had been selective in some studies, was tested.[29] Analyses of the BFM-83 and 87 protocols found evidence that the most important risk factor for treatment failure (death and lack of response) was leukocyte count.[23] The estimated probability of 5-year EFS was only 23% for patients with leukocyte counts above 100,000/mm³, in contrast with 48% for those with less than 100,000 leukocytes/mm³ (p = 0.0001). The absence of any statistical significance to the initial leukocyte analysis among the current sample may be due to the limited number of cases where leukocytes were above 100,000/mm³, just 12 children.

Nutritional variables did not influence prognosis in this study. Research performed in El Salvador and Recife with children treated for a number of different types of cancer, including AML, also failed to find statistical differences between malnourished and well-nourished patients.[30] Studying lymphoblastic leukemia, Viana et al.[31] showed that both malnutrition and poor socio-economic conditions were associated with worse prognosis. An analysis of the influence of nutritional and socio-economic factors has not been reported in international literature.

The use of VP-16 was introduced, in a randomized manner, between December/1992 and June/1999, in an attempt to achieve better results than those obtained with the classical induction scheme for AML (cytarabine + anthracycline). Worse results were observed among the patients who received etoposide, which does not correspond with that observed in other trials. In the BFM-83 protocol, VP-16 was used in all cases. The probability of event-free survival at six years was 49%±4%.[13] The BFM-83 protocol was also used in England with 30 patients.[32] The global probability of survival at five-years was 47%±20%. The *Children's Cancer Group* protocol number 213 randomized the induction of a group using cytarabine and daunorrubicin,

and another which received VP-16, thioguanine and dexamethasone in addition.[3] There was no statistically significant difference if global 5-year survival probability between the two groups (41% ± 6% for those treated with cytarabine and daunorrubicin, and 37%±6%, for those who received all five drugs, p = 0.16). A trial performed of the Medical Research Council-10 also randomized induction: in addition to cytarabine and daunorrubicin, one group received thioguanine and another etoposide.[25] The probability of 7-year event-free survival was 48% for patients who received thioguanine and 45% for the others (p = 0.5).

A satisfactory explanation has not been found for what was observed in this study. One hypothesis is that VP-16 may lead to a longer period of aplasia. The child would then take longer to fulfill laboratory criteria for the start of the consolidation phase. This hypothesis, however, was not confirmed because times for bone marrow recovery after induction were no different. The ages of the groups at diagnosis and initial leukocyte analyses were also no different statistically.

In conclusion, the present study has demonstrated that the accumulation of experience in the treatment of a complex disease in conjunction with the adoption of a unified treatment protocol make possible accentuated increases in prolonged remission for children with AML. Even so, an elevated frequency of deaths during induction provoked by infections explains the results of the trial, inferior to those achieved by the BFM group. The addition of etoposide to the remission induction method worsened, by an unexplained means, the prognosis of the children who received it.

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