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Survival evaluation of children with acute lymphoblastic leukemia treated with Berlin-Frankfurt-Munich trial

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Abstract

Objective: To determine the survival rate of children with acute lymphoblastic leukemia treated in Hospital São Lucas - Pontifícia Universidade Católica - Rio Grande do Sul during the past 10 years. To evaluate well known prognostic factors and to compare results of BFM 90 and 95 trials.

Methods: Mixed cohort study of 0 to 15-years-old children treated with BFM 90 and 95 trials during the past 10 years at Hospital São Lucas - Pontifícia Universidade Católica - Rio Grande do Sul. Data were obtained from medical records. The occurrence of death was described by Kaplan-Meier survival curves. The overall effect of the prognostic factors was evaluated using the Cox's multivariate model.

Results: Sixty three patients, whose mean age (standard-deviation) was 6.3±4.2 years, were included. Thirty five patients (55.6%) were female. The estimated probability of relapse free survival at 5 years (standard-error) was 50.8±7.2% for all patients, with 77.7±9.9% in the standard risk group, 41.3±15.4% in the intermediate risk group, and 39.3±13.7% in high risk group.

Conclusions: The estimated probability of relapse free survival was below the results in developed countries. However the standard risk group obtained better prognostic but the small number of the cases doesn't allow permanent conclusions.

J Pediatr (Rio J) 2003;79(2):149-58: Leukemia, lymphocytic, acute; survival analysis.

Introduction

Acute lymphoblastic leukemia (ALL) is responsible for around 80% of acute infant leukemia.[1,2] Peak incidence occurs between 2 e 5 years of age, its etiology is unknown.[3,4]

Currently, with the use of intensive chemotherapy and with increases in support therapies such as blood transfusions and antibiotic therapy, around 70 to 75% of affected children can be cured with present treatment protocols.[1,5,6] One of the most well-known protocols internationally is that developed by the German Berlin-Frankfurt-Munich (BFM) group.[7-9] This protocol uses patient stratification according to risk groups for the occurrence of relapse. The patients with the highest risk are treated with the most intensive chemotherapy. The treatment includes four phases: induction of remission, consolidation, maintenance and central nervous system prophylaxis (CNS). The primary objective of the treatment is to induce complete remission, i.e. reach levels of blasts in the bone marrow of less than 5%, and to restore

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normal hematopoiesis. Soon after, the consolidation phase is begun, the objective of which is to reduce the residual disease to a minimum (the presence of leukemia cells is undetectable with an electron microscope) and adjust the intensity of the treatment according to the relapse risk stratification. The BFM protocol uses the technique known as re-induction during consolidation phase, which consists of the use of the same drugs administered during the induction phase. Next maintenance therapy is performed, the object of which is to eradicate residual leukemia cells. During this phase the chemotherapy is less intensive. Prophylaxis of the CNS is begun during the induction phase and includes both chemotherapy and radiotherapy.

We determined the estimated probability of survival of children with ALL treated with the BFM protocol BFM at the Hospital São Lucas of the Pontifícia Universidade Católica do Rio Grande do Sul (HSL-PUCRS) during the period from 1991 to 2001. We also compared the survival of children treated with the BFM 90 and BFM 95 protocols, making adjustments for potential confusion factors.

Methods

Sixty-three patients diagnosed with ALL at ages of between 0 and 15 years, cared for at the HSL-PUCRS during the period between June 1991 and June 2001 and treated with the BFM protocol BFM were included in the study.

The BFM 90 and BFM 95 protocols are shown in Tables 1 and 2, respectively.

The BFM 95 protocol is a modification of the BFM 90 protocol. During the induction phase, there is a reduction of two doses of daunorubicin, a reduction of the L-asparaginase dose and an increase in the number of times that intrathecal methotrexate is administered to patients with CNS involvement. The re-induction phase is also administered to patients with intermediate risk and there is an increase in the number of times that intrathecal methotrexate is administered to patients with CNS involvement The modifications to the high risk blocks are: the application of 6 blocks instead of nine (each block is administered twice) 6-mercaptopurine is no longer administered during block HR1'; cyclophosphamide and mesna are increased for block HR1'; L-asparaginase is now infused over six hours instead of administered via intramuscular injection; there is an increase in the dose of ifosfamide and a reduction in the daunorubicin dose administered in block HR2'; and a reduced dose of etoposide in block HR3'. During the maintenance phase, children classified as low risk now have 156 weeks' treatment. The consolidation phase is unchanged from BFM 90. The modifications relating to intercranial radiotherapy are: prophylactic radiotherapy (12 Gy) is no longer performed with patients with an intermediate risk of relapse, unless there is T immunology; there is a reduced therapeutic irradiation dosage from 24 Gy to 18 Gy, with the exception of children aged $\geq$ 1 year and < 2 years, who receive 12 Gy.

As criteria for the stratification into risk groups, known as the risk factor, the BFM 90 protocol uses; the degree to which the CNS is compromised; T cell immunology; the presence of t (9,22) or the BCR-ABL fusion; the number of blasts per micro liter of blood on the 8th day of treatment (D8); and the remission status on the 33rd day of treatment (D33). The low risk group included children fitting the following criteria: risk factor < 0.80; absence of CNS involvement; absence of T immunology; absence of t(9;22); < 1,000 blasts/µl on D8; and complete remission on D33. Fulfilling the following criteria a child is classified as having intermediate risk: risk factor 0.80; risk factor < 0.80 but with CNS involvement or with T immunology; absence of t (9,22); < 1,000 blasts/µl in peripheral blood at D8; and complete remission on D33. The high risk group includes children with t (9,22); with > 1,000 blasts/µl in peripheral blood at D8; with CNS involvement on the 29th day of treatment; and with > 5% of blasts in the bone marrow on D33.[7]

Using the BFM 95 protocol, patients are stratified based on the following criteria: number of leukocytes per micro liter in the peripheral blood at diagnosis; T cell-classed immunology; the presence of t (9,22) or the BCR-ABL fusion, or t (4,11) or the MLL-AF4 fusion; the number of blasts per micro liter in peripheral blood at D8; the remission status on D33. In contrast to BFM 90 protocol, initial CNS involvement does not justify classification in the intermediate or high risk groups. For a classification of low risk, all of the following criteria must be fulfilled: age $\geq$ 1 year and < 6 years at diagnosis; < 20,000 leukocytes/µl at diagnosis; the absence of T cell immunology; the absence of t (9,22) or of the BCR-ABL fusion; the absence of t (4,11) or the MLL-AF4 fusion; < 1,000 blasts/µl in peripheral blood at D8; and complete remission at D33. To be classified at intermediate risk all of the following criteria must be fulfilled: the absence of t (9,22) or the BCR-ABL fusion; the absence of t (4,11) or the MLL-AF4 fusion; < 1,000 blasts/µl in peripheral blood at D8; and complete remission at D33. Additionally, there should be one of the following: age < 1 year or 6 years at diagnosis; a count of $\geq$ 20,000 leukocytes/µl at diagnosis. For a classification of high risk all of the following criteria must be fulfilled, in isolation, irrespective of age and initial leukocytes count: blast count $\geq$ 1,000/µl at D8; the absence of complete remission on D33; the presence of (9,22) or of the BCR-ABL fusion; or the presence of t (4,11) or the MLL-AF4 fusion.

A mixed cohort study was performed using information deriving from medical records. Quantitative data was described using averages and standard deviations in cases of asymmetry descriptions were made using median averages and the interquartile range (P25 to P75). For categorical variables frequency and percentages were used.

To describe the incidence of disease-free survival and of death between the groups, incidence density was

Table 1 - BFM 90 trial

Drug	Dose administration route	Treatment day
Induction		
Trial		
Phase A		
– prednisone	60 mg/m^2 O	1-28
		1-21 (high risk)
– vincristine	1.5 mg/m^2 (up to 2 mg) IV	8, 15, 22, 29
– daunorubicin	30 mg/m^2 IV	8, 15, 22, 29
– L-asparaginase	10,000 U/m^2 IV	8, 12, 15, 18, 21, 24, 27, 30, 33
		8, 12, 15, 18, 21, 24, 27 (high risk)
– methotrexate	6-12 mg IT*	1, 15, 29
		1, 8, 15, 22, 29 (CNS+)
Phase B**		
– mercaptopurine	60 mg/m^2 O	36-64
– cyclophosphamide (+ mesna***)	1,000 mg/m^2 IV	36, 64
– cytarabine	75 mg/m^2 IV (in 30 min)	38-41, 45-48, 52-55, 59-62
– methotrexate	6-12 mg IT*	45, 59
Consolidation**		
Trial M		
– mercaptopurine	25 mg/m^2 O	1-56
– methotrexate (+ pholinic ac.$^{\&}$)	5,000 mg/m^2 IV (in 24 h)	8, 22, 36, 50
– methotrexate	6-12 mg IT*	8, 22, 36, 50
Re-induction$^{\&\&}$		
Trial II		
– dexamethasone	10 mg/m^2 O	1-21
– vincristine	1.5 mg/m^2 (up to 2 mg) IV	8, 15, 22, 29
– doxorubicin	30 mg/m^2 IV	8, 15, 22, 29
– L-asparaginase	10,000 U/m^2 IV	8, 11, 15, 18
– cyclophosphamide (+ mesna***)	1,000 mg/m^2 IV	36
– cytarabine	75 mg/m^2 IV (in 30 min)	38-41, 45-48
– thioguanine	60 mg/m^2 O	36-49
– methotrexate	6-12 mg IT*	38, 45
Intensive consolidation$^{\&\&\&}$		
Block HR1		
– dexamethasone	20 mg/m^2 O	1-5
– mercaptopurine	100 mg/m^2 O	1-5
– vincristine	1.5 mg/m^2 (up to 2 mg) IV	1,5
– methotrexate (+pholinic ac.$^{\&}$)	5,000 mg/m^2 IV (in 24 h)	1
– cytarabine	2,000 mg/m^2 IV (12/12 h)	5
– L-asparaginase	25,000 U/m^2 IM	6
– methotrexate	6-12 mg IT*	1
– cytarabine	16-30 mg IT$^{\#}$	1
– prednisolone	4-10 mg IT$^{\#\#}$	1
Block HR2		
– dexamethasone	20 mg/m^2 O	1-5
– thioguanine	100 mg/m^2 O	1-5
– vindesine	3 mg/m^2 (up to 5 mg) IV	1
– methotrexate (+pholinic ac.$^{\&}$)	5,000 mg/m^2 IV (in 24 h)	1
– iphosphamide	400 mg/m^2 IV (in 1 h)	1-5
– daunorubicine	50 mg/m^2 IV (in 24 h)	5
– L-asparaginase	25.000 U/m^2 IM	6
– methotrexate	6-12 mg IT*	1
– cytarabine	16-30 mg IT$^{\#}$	1
– prednisolone	4-10 mg IT$^{\#\#}$	1

Table 1 - BFM 90 trial

Drug	Dose administration route	Treatment day
Block HR3		
– dexamethasone	20 mg/m^2 O	1-5
– cytarabine	2,000 mg/m^2 IV (12/12 h)	1, 2
– etoposide	150 mg/m^2 IV (in 1 h)	3-5
– L-asparaginase	25,000 U/m^2 IM	6
– methotrexate	6-12 mg IT*	5
– cytarabine	16-30 mg IT#	5
– prednisolone	4-10 mg IT##	5
Maintenance###		
– mercaptopurine	50 mg/m^2/day O	
– methotrexate	20 mg/m^2/week O	

O: oral, IV: intravenous, IT: intrathecal, IM: intramuscular, CNS: central nervous system.

* According to age: < 1 year, 6 mg; ≥ 1 year and < 2 years, 8 mg; ≥ 2 years and < 3 years, 10 mg; ≥ 3 years, 12 mg.
** Only for low and intermediate risk.
*** Mesna is used after the administration of cyclophosphamide for prophilaxis of hemorrhagic cystitis.
& Pholinic acid is administered to help the release of methotrexate.
&& Only for low risk.
&&& Only for high risk. Each block is repeated twice in the following order: HR1, HR2 and HR3.
# According to age: < 1 year, 16 mg; ≥ 1 year and < 2 years, 20 mg; ≥ 2 years and < 3 years, 26 mg; ≥ 3 years, 30 mg.
According to age: < 1 year, 4 mg; ≥ 1 year and < 2 years , 6 mg; ≥ 2 years and < 3 years , 8 mg; ≥ 3 years, 10 mg.
Doses are adjusted according to the leucocytes count. For all patients, the maintenance lasts up to 24 months of treatment (starting at trial I).

used, comparing groups for incidence density and confidence interval, with significance determined by the chi-square test. Survival analysis as proposed by Kaplan-Meier was used.[10] In order to control the effect of the multiple factors considered by this study, the multivariable proportional hazards regression technique was used (Cox regression).[11] For bi-variable analysis alpha error probability of 0.05 was adopted, and, for the multivariable regression, 0.10. Data was processed and analyzed using SPSS version 9.0.

This research project was approved by the Scientific Commission of the Medical Faculty and the Commission for Ethics in Research, both of the HSL-PUCRS. Dispensation was solicited from the informed patient consent form. The authors signed an undertaking to maintain confidentiality in the use of data. The informed patient consent form to allow the children to be subjected to chemotherapy treatment was signed by a parent or guardian and is to be found in their medical records.

Results

Of the 63 patients in the study, 35 (55.6%) were female. The average age (±SD) was 6.3±4.2 years giving a median (25th p to 75th p) of 5 years (3 to 9). The median (25th p to 75th p) of the period for which survivors were observed was 3.8 years (1.2 to 8.5). The distribution of patients across the risk groups was uniform: 22 (34.9%) were low risk; 23 (36.5%), intermediate risk; and 18 (28.6%), high risk (Table 3).

The median (25th p to 75th p) of the leukocytes counts at diagnosis and verified was 8,700/ µl (3,800/µl to 29,900/µl). The majority of patients reached blast count levels < 1,000/µl at D8: 95% in the BFM 90 group and 82.6% in the BFM 95 group. The same occurring for remission at D33: 92.5% in the BFM 90 group and 95.7% in the BFM 95 group.

The total number of deaths was 23, occurring over a 10 year period of observation. The global estimated probability of survival for five years (±SE) was 56.5±7.5%. Survival for five years free of the disease (±SE) was 50.8±7.2%, being 77.7±9.9% for the low risk group; 41.3±15.4% for the intermediate risk group; and 39.3±13.7% for the high risk group. Figure 1 illustrate the global survival and disease-free survival of the patients studied.

On comparing the survival curves for patients treated with the BFM 90 protocol with those treated with BFM 95, it can be observed that the global estimated probability of survival for five years (±SE) were around 57±9% and 66±11%, respectively. This difference did not attain statistical significance in the analysis by the log rank test (p = 0.714). Such a comparison can be found in Figure 2.

Table 2 - BFM 95 trial

Drug	Dose and administration route	Treatment day
Induction		
Trial		
Phase A		
– prednisone	60 mg/m² O	1 - 36
		1-30 (high risk)
– vincristine	1,5 mg/m² (up to 2 mg) IV	8, 15, 22, 29
– daunorubicine	30 mg/m² IV	8, 15, 22, 29
		8, 15 (low risk)
– L-asparaginase	10,000 U/m² IV	12, 15, 18, 21, 24, 27, 30, 33
		12, 15, 18, 21, 24, 27 (high risk)
– methotrexate	6 - 12 mg IT*	1, 12, 33
		1, 12, 18, 27, 33 (CNS+)
Phase B**		
– mercaptopurine	60 mg/m² O	36 -63
– cyclophosphamide (+ mesna***)	1,000 mg/m² IV	36, 64
– cytarabine	75 mg/m² IV (in 30 min)	38-41, 45-48, 52-55, 59-62
– methotrexate	6 - 12 mg IT*	45, 59
Consolidation**		
Trial M		
– mercaptopurine	25 mg/m² O	1 - 56
– methotrexate (+ pholinic ac.[&])	5,000 mg/m² IV (in 24 h)	8, 22, 36, 50
– methotrexate	6 - 12 mg IT*	8, 22, 36, 50
Reinduction		
Trial II		
– dexamethasone	10 mg/m² O	1 - 31
– vincristine	1.5 mg/m² (up to 2 mg) IV	8, 15, 22, 29
– doxorubicine	30 mg/m² IV	8, 15, 22, 29
– L-asparaginase	10,000 U/m² IV	8, 11, 15, 18
– cyclophosphamide (+ mesna***)	1,000 mg/m² IV	36
– cytarabine	75 mg/m² IV (in 30 min)	38 - 41, 45 - 48
– thioguanine	60 mg/m² O	36 - 49
– methotrexate	6 - 12 mg IT*	38, 45
		1, 18, 38, 45 (CNS+)
Intensive consolidation[&&&]		
Block HR1		
– dexamethasone	20 mg/m² O	1 - 5
– vincristine	1.5 mg/m² (up to 2 mg) IV	1, 6
– cytarabine	2,000 mg/m² IV (12/12 h)	5
– methotrexate (+pholinic ac.[&])	5,000 mg/m² IV (in 24 h)	1
– cyclophosphamida (+ mesna***)	200 mg/m² IV (12/12 h)	2 - 4
– L-asparaginase	25,000 U/m² IM	6
– methotrexate	6 - 12 mg IT*	1
– cytarabine	16 - 30 mg IT[#]	1
– prednisolone	4 - 10 mg IT[##]	1
Block HR2		
– dexamethasona	20 mg/m² O	1 - 5
– vindesine	3 mg/m² (up to 5 mg) IV	1, 6
– daumorubicine	30 mg/m² IV	5
– methotrexate (+ pholinic ac.[&])	5,000 mg/m² IV (in 24 h)	1
– iphosphamide (+ mesna***)	800 mg/m² IV (12/12 h)	2 - 4
– L-asparaginase	25,000 U/m² IV	6
– methotrexate	6 - 12 mg IT*	1
		1, 5 (CNS+)
– cytarabine	16-30 mg IT[&&&]	1
		1, 5 (CNS+)
– prednisolone	4 - 10 mg IT[#]	1
		1, 5 (CNS+)

Table 2 - BFM 95 trial

Drug	Dose and administration route	Treatment day
Block HR3		
– dexametasone	20 mg/m² O	1 - 5
– cytarabine	2,000 mg/m² IV (12/12 h)	1, 2
– etoposide	100 mg/m² IV (in 1 h)	3, 5
– L-asparaginase	25.000 U/m² IM	6
– methotrexate	6 - 12 mg IT*	5
– cytarabine	16 - 30 mg IT#	5
– prednisolone	4 - 10 mg IT##	5
Maintenance###		
– mercaptopurine	50 mg/m²/day O	
– methotrexate	20 mg/m²/week O	

O: oral, IV: intravenous, IT: intrathecal, CNS: central nervous system.
* According to age: <1 year, 6 mg; ≥ 1 year and < 2 years, 8 mg; ≥ 2 years and < 3 years, 10 mg; ≥ 3 years, 12 mg.
** Only for low or intermediate risk.
*** Mesna is used after the administration of cyclophosphamide for prophylaxis of hemorrhagic cystitis.
& Pholinic acid is administered to help to realease methotrexate.
&& Only for high risk. Each block is repeated once in the following order: HR1', HR2' and HR3'.
&&& According to age: <1 year, 16 mg; ≥ 1 year and < 2 years, 20 mg; ≥ 2 years and < 3 years, 26 mg; ≥ 3 years, 30 mg.
# According to age: < 1 year, 4 mg; ≥ 1 year and < 2 years, 6 mg; ≥ 2 years and < 3 years, 8 mg; ≥ 3 years, 10 mg.
Doses are adjusted according to leukocytes count. The maintenance lasts up to 24 months of treatment (starting at trial I). For boys classified as low risk, the treatment lasts up to 156 months.

From among the varied factors studied it is possible to highlight a more accentuated effect among the intermediate and high risk groups when compared with the low risk group. In Figure 3, the difference between the survival rates experienced by members of the subgroups defined by risk classification according to the BFM protocol.

Another important factor was the presence of > 20,000 leukocytes/µl on diagnosis, which presented a relative risk of 2.7 and significance of 0.020. A blast count ≥ 1,000/µl at D8 was also a factor which stood out, presenting a relative risk of 3.3 (p = 0.056). Other factors did not demonstrate important effects.

Table 3 - Comparison of basic characteristics and relevant clinical results between the treatment protocols in patients with acute lymphocytic leukemia

Variable	Total n = 63	BFM 90 n = 40	BFM 95 n = 23	p
Age, years	6.3 ± 4.2	6.0 ± 3.8	6.7 ± 4.8	
Female, n	35 (55.6%)	21 (52.5%)	14 (60.9%)	0.704
Follow up period, years				
deaths	0.96 (0.24 to 2.49)	1.23 (0.51 to 3.50)	0.24 (0.16 to 1.07)	
survivals	3.81 (1.22 to 8.58)	6.36 (1.71 to 9.47)	1.78 (0.95 to 3.50)	
total	1.94 (0.73 to 4.53)	3.70 (0.96 to 9.58)	1.41 (0.49 to 2.82)	
Risk group, n				
low	22 (34.9%)	18 (45.0%)	4 (17.4%)	
intermediate	23 (36.5%)	12 (30.0%)	11 (47.8%)	
high	18 (28.6%)	10 (25.0%)	8 (34.8%)	
Patients-year under risk	208.72	171.09	37.63	
Deaths (x100 pac-year)	11.0	9.4	18.6	

Data are presented as frequency (%), mean (SD) and median (25th p to 75th p).

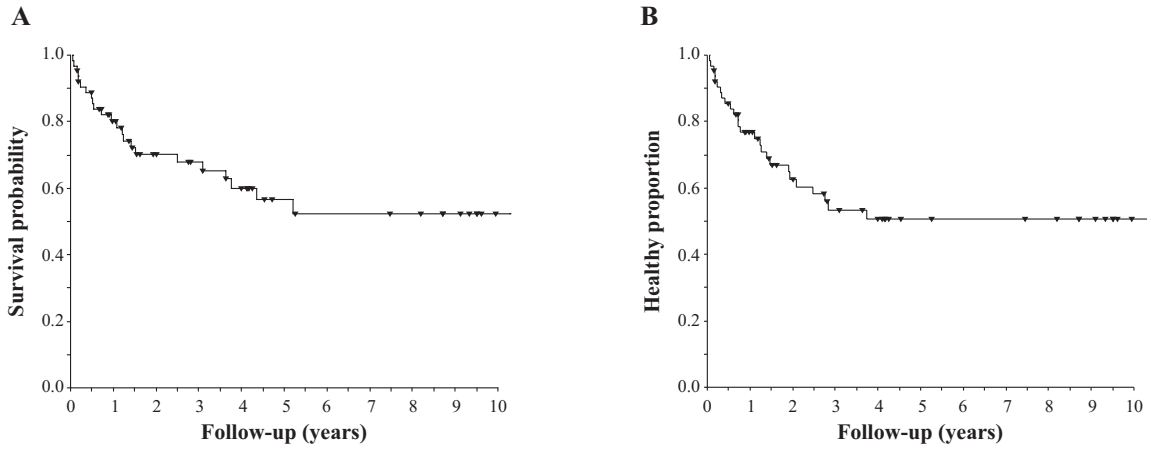

Figure 1 - Kaplan-Meier curves describing the total healthy survival rate in the patients

After adjusting for potential confusion factors, the BFM 90 protocol showed a small excess of the occurrence of deaths, expressed by a relative risk of 1.8. Nevertheless, in the present study this finding does not have statistical significance (Table 4). A higher mortality was observed among the intermediate and high risk groups with relation to the low risk, and a higher risk among patients with a leukocyte count of $\geq$ 20,000/µl on diagnosis (RR = 2.3 and p = 0.102). After analysis using the Cox model, the blast count at D8 lost statistical significance, the relative risk being 2.6 (p = 0.251).

Table 4 - Relative risk of death according to chemotherapy protocols for acute lymphocytic leukemia

Variable	n	RR*	90%CI	p
Protocol				
BFM90	40	1.8	0.7 to 4.5	0.300
BFM95	23			

* Relative risk from multivariate regression model of Cox's proportional hazards adjusted for the effects of the risk groups (low, intermediate and high), sex, age on diagnosis, leukocytes inital count, blasts count in D8 and immunophenotype.

Discussion

In this study we found that the global estimated probability of disease-free survival for five years was lower than that achieved by treatment protocols conducted in the United States and in Europe. The German-Swiss-Austrian study group responsible for BFM 90, published that disease-free survival for six years 6 years (±SE) was 78±1% among the 2,178 patients studied.[8] In a study performed by the Associazione Italiana Ematologia Oncologia Pediátrica (AIEOP), disease-free survival for five years (±SE) was 71±1.4%. The protocol used was AIEOP-ALL 91, based on the BFM protocol, and 1,194 children were treated between 1991 and 1995.[12] The Pediatric Oncology Group (POG) described a rate of disease-free survival for five years of approximately 71% among their 3,825 patients.[13] Although conducted with fewer patients, just 366, the St. Jude Children's Research Hospital (SJCRH) study performed between 1991 and 1997, described disease-free survival for five years (±SE) at 81±8%.[14] For 377 patients studied the treatment protocol used by the Instituto do Câncer Dana-Farber, obtained a level of disease-free survival for five years (±SE) of 83±2% in their most recent study conducted between 1991 and 1995.[15] The worst results were obtained by the English group United Kingdom Acute Lymphoblastic Leukemia (UKALL) which, with 2,090 patients treated with their treatment protocol UKALL XI, obtained a disease-free survival for five years rate (±SE) of 64±5%.[16]

In developing countries the results are more modest. In a study conducted by an Argentine group into the treatment of ALL in infancy a disease-free survival for five years level (±SE) of 64±5% was obtained across their 885 patients between 1990 and 1995. The protocol used by this group is similar to the BFM 90, except for small modifications to the consolidation phase.[7] In Brazil, Viana et al. found disease-free survival (±SE) at 58 at 40±6% analyzing 128 children.

The authors related these results to socio-economic factors.[9]

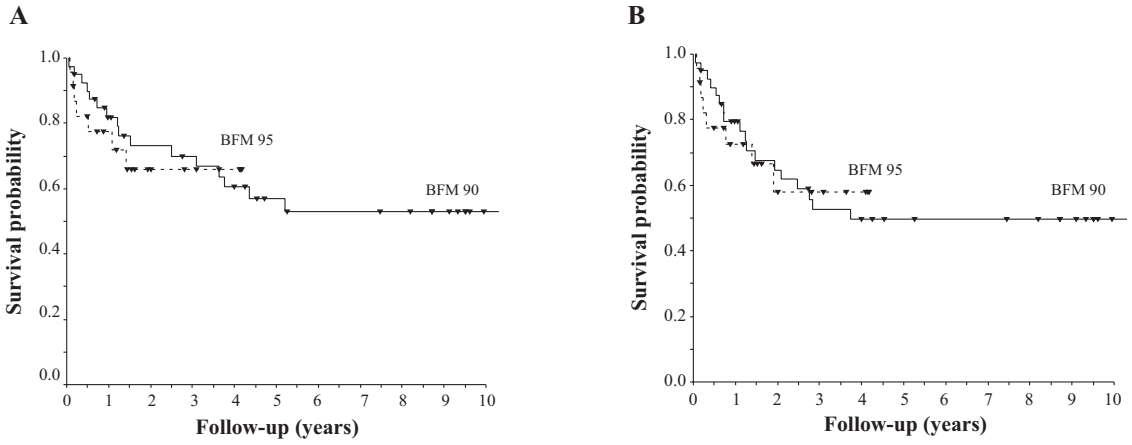

Figure 2 - Kaplan-Meier curves describing the total survival rate and the healthy survival rate in the patients according to the treatment protocol

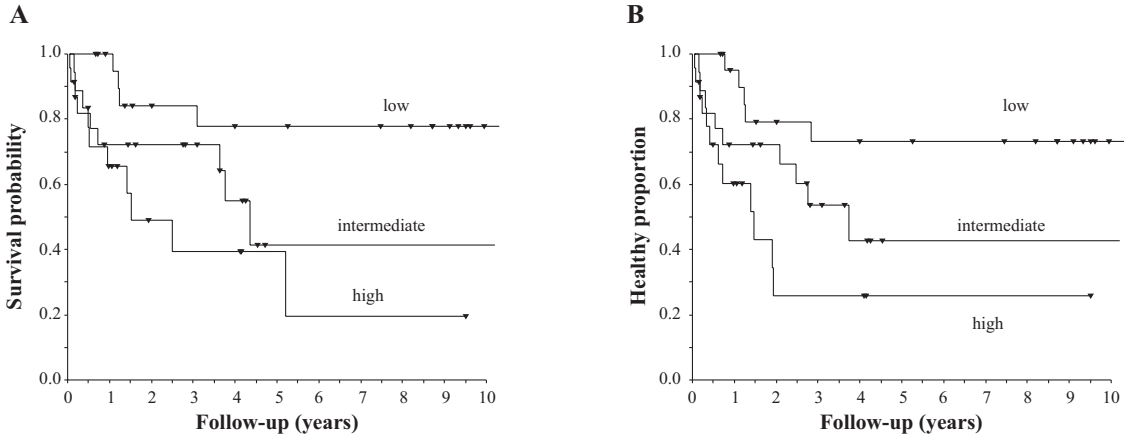

Figure 3 - Kaplan-Meier curves describing the global survival rate and the healthy survival rate in the patients according to the separation in risk groups

The analysis of disease-free survival according to the stratification of patients into risk groups for the BFM 90 group show that the intermediate and low risk groups achieved 85±2% and 83±2% disease-free survival over 6 years (±SE), respectively. Meanwhile the high risk group had a rate of disease-free survival after 6 years (±SE) of only 34±3%, due to the much greater number of systemic relapses.[8] In the AEIOP-ALL 91 study, the results were similar: disease-free survival for 5 years (±SE) for the low risk group was 83±5%; for the intermediate risk group it was 75±4%; and for the high risk group it was 40±7%.[12] In our study the observed survival level for the low and high risk groups was comparable to that observed in the European studies described above. However the survival rates achieved by the intermediate risk group was much lower than those of other studies, being almost equal to that of the high risk group. This is relevant since, in the bivariate analysis, the risk stratification showed itself to be the most important factor which respect of the occurrence of deaths (intermediate risk group: RR = 4.4 and p = 0.014; high risk group: RR = 7.8 and p < 0.001). The risk stratification, after multivariate adjustment for potential confusion variables continued to be the most important factor for prognosis. The intermediate risk and high risk groups proved to be similar (intermediate risk group: RR = 3.7 and p = 0.065; high risk group: RR = 2.2 and p = 0.267). As the chemotherapy and their dosages used with the low and intermediate risk groups are similar, the stratification does not appear, by itself, to justify the difference observed.[7,8,12]

In the first analysis of the distribution of the risk groups across the BFM 90 and BFM 95 protocols, we can note that there is a predominance of intermediate and

high risk patients in the BFM 95 (Table 3), despite this difference not attaining classical significance (p = 0.084). It is possible to infer that this distribution of the patients across the risk groups could have had an influence over the results produced by the bivariate analysis for occurrence of death, in which the BFM 90 protocol demonstrated a mild protector effect in relation to the BFM 95, expressed by a RR of 0.5 despite being statistically insignificant The results of this analysis could have suffered from the effects of the high incidence of patients-year and of the low number of patients using the BFM 95. Nevertheless, when adjustments are made for confusion factors in the proportional hazards regression, the protector effect of BFM 90 disappears, and it even acquires a mild risk factor (Cox model) (RR = 1.8 and p = 0.300). There are currently insufficient results available in relevant literature on the BFM 95 protocol to enable us to discuss them here.

An early response to treatment is considered the strongest prognosis factor with relation to the treatment.[17,18] In the BFM protocol the reduction of the peripheral blast count to < 1,000/µl after 7 days' use of prednisone and one dose of intrathecal methotrexate, proved to be the single most important prognosis factor.[19] In addition to this, the achievement of remission status at the end of the induction course constitutes an important prognosis factor, and is verified in the BFM protocols by means of the morphological analysis of the bone marrow and of the cerebrospinal fluid on D33. Together, the two measurements can provide prognostic information within a classification system which can be easily adopted by centers, such as ours, which do not yet have the technology available to routinely measure the minimal residual disease.[20] We have shown that there was no difference between the BFM 90 and 95 protocols in relation to blast counts of ≥ 1,000/µl on D8 or remission status at D33.

The BFM protocol also stratifies patients by their initial leukocytes counts: > or < 20,000/µl at diagnosis. High counts are related with adverse results, the number of leukocytes has shown itself an important prognostic factor in our study, surpassed only by the stratification into risk groups.

The limitations of this study are the result of the low number of patients it includes. With the exception of the variables risk group and number of leukocytes, no variable produced significant results.

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