The Impact of Acute Lymphoblastic Leukemia Treatment on Central Nervous System Results in Bogota, Colombia

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Summary: To improve the outcome of children with acute lymphoblastic leukemia (ALL) treated at the National Cancer Institute, Bogota, Colombia, a protocol based on the BFM-90 (Berlin, Frankfurt, Munster study) and the LSA_2L_2 regimens was implemented in the year 1993. The patients were classified as being standard risk (SR) or high risk (HR) according to clinical criteria, to which cytogenetic information and day-8 prednisone response were also added. A 123-patient cohort entered the study, 18 of them being considered SR and 105 HR. There was a 94% 10 years' event-free-survival rate for the SR group and 36% for the HR group. Decreased induction death rate (7% vs. 14%), increased complete remission (CR) rate (81% vs. 75%), and continuous CR (45% vs. 33%) were found in comparison with the previous study. A significant improvement was achieved in relapse rate, 44% to 28% ($P = 0.029$), mainly due to reduced central nervous system relapse rate from 16% to 6% ($P = 0.037$), whereas the number of patients receiving cranial radiation was reduced to 55%. A major problem concerned the increased CR mortality rate, 5% to 14% ($P = 0.06$). Improved supportive care therapy and socioeconomic conditions will hopefully reduce the CR mortality rate in the future.

Key Words: pediatric ALL, developing country, CNS-leukemia, intensive chemotherapy

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The outcome of children suffering from acute lymphoblastic leukemia (ALL) has markedly improved with modern therapy, reaching a 5-year event-free survival (EFS) rate of 80% in industrialized countries.[1–7] These advances are mostly attributed to intensive chemotherapy.[2,3,5,7] However, results remain poor in low income countries (LIC), major obstacles being the frequency of late diagnosis and difficulties or limitations in delivering intensive chemotherapy.

In an effort to improve the survival of children suffering from ALL who are being treated at the National Cancer Institute in Bogotá, Colombia (NCI-BC),[8] a treatment protocol was designed on the basis of 2 highly successful chemotherapeutic regimens: BFM-90 (Berlin, Frankfurt, Munster study) and LSA_2L_2. Prednisone response (PR)[2,3] was evaluated and cytogenetic analysis[9] was introduced to improve our ALL patient population's risk classification.

Because of a high incidence of central nervous system (CNS) relapse having been experienced with a previous protocol, one of the present study's main objectives was to reduce meningeal relapse incidence. Using dexamethasone (DXM) during induction, moderate dose methotrexate infusion[2,3,10,11] and extended doses of triple intrathecal (TIT) chemotherapy[12,13] were thus introduced. Reducing cranial radiation therapy (CRT) or omitting it[7,12,14] to avoid late toxicity or secondary neoplasm also became part of this study.

This paper reports the long-term follow-up of patients who entered the study and how our results were compared with a previous study[8] carried out at the NCI-BC.

PATIENTS AND METHODS

Patients and Diagnostic Work-up

The study population consisted of 123 consecutive, previously untreated children with non-B ALL aged up to 16 years, who had been diagnosed at the NCI-BC from January 1, 1993 to December 31, 1995.

A diagnosis of ALL was based on French-American-British (FAB) criteria.[15] The BFM index[2,3] and presence of extramedullary leukemia was established from the physical examination made on admission; cerebrospinal fluid (CSF) cytospin cytology, pertinent laboratory and imaging studies, and bone marrow (BM) chromosomal analysis[16] were carried out for each patient.

Sixty percent of the patients were outside Bogota and most of them came from low income families.

The study was approved by the NCI-BC Institutional Review Board and informed written consent was obtained from all of the patients' parents.

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Definitions

The standard risk (SR) criteria included being aged 2 to 9 years, having BFM index < 0.8, a cerebro spinal fluid proving clear of lymphoblasts and < 5 cells/mm^3, no thymic or testicular enlargement, good day-8 PR, complete BM remission on day 36, and normal or hyperdiploid karyotype. Patients who did not fulfill one or more of these criteria or who had leukemia-lymphoma syndrome were classified as high risk (HR).

Day-8 PR was evaluated by peripheral blood white blood cell (WBC) count and morphology. A good PR was considered to be < 1000 blast cells/μL as opposed to poor PR defined as being ≥ 1000 blast cells/μL.[2,3] BM induction remission was evaluated on day 36 using previously established criteria.[4]

Meningeal leukemia was defined as being the presence of 5 or more leukocytes/μL plus unequivocal evidence of lymphoblasts in CSF cytology.

Simultaneous relapse occurring at 2 or more sites was considered as being a combined relapse.

BM having a low (or absent) mitotic index or poor chromosomal morphology despite adequate sampling and preservation was classified as being cytogenetic failures.

Treatment Protocol

Treatment was based on the BFM-90 protocol[2] (Fig. 1), which was selected because of NCI-BC personnel's previous experience with this regimen and the improved results obtained by using it when compared with historical controls.[8]

Prephase therapy consisted of administering prednisone from days 1 to 8 and the first dose of TIT on day 8 of protocol I. SR patients were programmed to receive protocol I-M-II and oral maintenance, without using doxorubicin (ADR), cyclophosphamide (CPM), and prophylactic CRT. HR patients received full protocol I-M-II plus prophylactic CRT and maintenance therapy with 8 cycles of LSA_2L_2, as well as oral 6-mercaptopurine and methotrexato (MTX).

Some other modifications were introduced to the protocol in an effort to tailor therapy to the study population and local conditions. Oral DXM was used from day 9 to 28 during induction[17,18] to enhance CNS leukemia control. A 7-day rest period was introduced at the end of the second week of Ara-C therapy in protocol I to reduce life-threatening toxicity. Cyclophosphamide was omitted from protocols I and II and doxorubicin from protocol II for SR-patients to reduce or avoid long-term related toxicity. MTX infusion was reduced to a moderate 2.5 g/m^2 dose owing to an inability to measure the drug's serum level. HR-block elements 1, 2, and 3 were replaced by rotating pairs of drugs, according to the Pediatric Oncology Group's modified version of LSA_2L_2,[19] to complete 8 cycles administered every 8 weeks. The latter modification was introduced to overcome shortages in resources for obtaining all the chemotherapeutic agents used in the BFM-90 HR blocks and to administer them in an outpatient setting (day-hospital).

For administering protocol M therapy, patients received in-hospital hydration and urinary alkalinization starting 12 hours before MTX infusion, being maintained thereafter for 48 to 72 hours.[20] Calcium leucovorin rescue was provided 48 hours after beginning MTX infusion.[21]

CNS prophylaxis included 11 TIT administrations in protocol I, M, and II. SR and HR patients also received 6 and 8 TIT doses, respectively, during maintenance, complemented by prophylactic CRT (1800 cGy) for HR patients. Moreover, HR patients were individually assessed in an attempt to reduce late CNS toxicity and second malignancies[7,12–14]; CRT was omitted in all those having a good PR response, complete remission (CR) at the end of induction, and were aged less than 6 years.

Patients with CNS leukemia documented at diagnosis received 5 weekly TIT plus 2 additional doses during protocol I plus 2400 cGy cranial and 1800 cGy spinal fields, respectively, at the end of protocol II.

Supportive measures and parents or caregivers' education was provided, emphasizing prevention, early identification of complications, and nutritional support.

Follow-up

Patients in good clinical conditions continued their treatment as outpatients, whereas accommodation was offered to families living outside Bogota to ensure their adherence to protocol treatment. Patients were followed up in accordance with chemotherapy requirements, as established by the protocol. Children were seen every 4 to 8 weeks during maintenance, or earlier if necessary. Off-therapy follow-up was conducted quarterly during the first year, every 4 to 6 months for 1 more year, and yearly thereafter. Follow-up closure was determined to be December 3, 2004.

Statistical Analysis

EFS and overall survival (OS) were estimated by using the Kaplan-Meier method and EFS curves were compared by means of log-rank test. EFS was defined as being the time from diagnosis to the first adverse event or to the date of last follow-up.

Death during induction, failure to achieve CR, relapse at any site, death during CR, or developing a second malignancy were considered to be adverse events.

EFS distribution was calculated considering those who refused to continue treatment ($n = 5$) to have treatment failure, as of their last follow-up date.

OS was measured from the date of diagnosis to the last follow-up or death date, except for those who abandoned therapy. OS distribution for these patients was measured from patient diagnosis date to their estimated death date, obtained by calculating the median numbers of days between the last follow-up dates and the dates of deaths of those patients who were known to have died. The median (221 d) was then added to the last follow-up of each such patient to obtain the estimated dates of death.

PROTOCOL I (INDUCTION AND INTENSIFICATION)

```
PRED   PPP                                CPM   X                      X
DXM           LLLLLLLLLLLLLLLLiiiiiiiii   ARA-C LLLL    LLLL           LLLL   LLLL
VCR           X     X     X     X         6-MP  QQQQQQQQQQQ            QQQQQQQQQQQ
DNR           &     &     &     &
L-ASP               I  I  I  I  I  I

TIT           T           T               T                      T              T
BM                                        O
DAY    1      8     15    22     29       36    38 39-42  46-49,50, 53 ~ 62,63-64-66  69-72 76
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P Prednisone 60 mg/m2 orally, days 1 to 8
DXM (dexamethasone) 6 mg/m2 orally divided into three doses, day 9-29, then tapered over 7 days
L-ASP (L-asparaginase) 6.000 U/m2 IM, three times per week for 2 weeks
DNR (daunorubicin)
TIT: Cytarabine (ARA-C) age adjusted (aa): 15, 20, 25 and 30 mg for 1, 2 ,3 years and older, respectively, DXM: 4,4,8 and 8 (aa) and MTX: 6,8,10 and 12 mg(aa), days 8,22,36,50 and 64.
ARA-C(Cytarabine) 60 mg/m2 IV daily, divided into two phases each one of 14 days, introducing an interim rest period of 7 to 9 days.
6-MP (mercaptopurine) also divided into two phases.

PROTOCOL M (MEDIUM-HIGH DOSES OF MTX)

```
6-MP     LLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLL
HD-MTX            &               &                 &               &
CF                  IIIII           IIIII             IIIII           IIIII

TIT               T               T                 T               T
DAY      1        8               22                36              50    57
```

HD-MTX (medium high doses of MTX) 2.5 gm/m2/ IV, 24 hours infusion, 10% dose during the first hour and 90% during 24 hours. CF (Calcium leucovorin rescue) 15mg/m2, IV, 6 doses, every 6 hours, was given 48 hours after the start of the MTX IV infusion. TIT was applied after the 10% of HD-MTX.

PROTOCOL II (REINDUCTION AND REINTENSIFICATION)

```
DXM    LLLLLLLLLLLLLLLLLLLLiiiiiiiiiiiii      | CPM    X
VCR          X      X      X      X           | ARA-C  LLLL           LLLL
ADR          &      &      &      &           | 6-TG   OOOOOOOOOOOOOOOOOOO
L-ASP               I   I   I   I             | TIT     T              T

DAY    1     8      15     22     29          36,37- 40        43- 46       51
```

DXM (dexamethasone) 6 mg/m2 orally divided into three doses, day 1-21,then tapered over 7 days; L-ASP (L-asparaginase) 6.000 U/m2, IM, twice a week per 2 weeks.
ARA-C (Cytarabine) 60 mg/m2 IV, days 37-40 and 43-46, TIT days 37 and 43.
ADR (doxorubicin) and CPM (Cyclophosphamide) were given only for HR.

MAINTENANCE SR (STANDARD RISK)

```
6-MP   LLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLLL
MTX    * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
TIT    T       T       T       T       T       T
WEEK   28      36      44      52      60      68                       130
```

6-MP (mercaptopurine) 60mg/m2 orally, daily; MTX (Methotrexate) 20 mg/m2, orally, once a week, both were given at night, 2 hours after the last meal.

MAINTENANCE HR LSA2L2 (HIGH RISK)

```
 CPM   IIII          HY IIII      MTX   IIII      ARA-C IIII
6-TG     &          DNR   &     BCNU     &          VCR   &

TIT      T                T               T                T
6-MP        LLLLLLLL       LLLLLLLL       LLLLLLLL        LLLLLLLL LLLLLLLLLLLL
MTX         * * * * * *    * * * * * *    * * * * * *     * * * * * *  * * * * * * * * * * *

CRT    H
WEEK 28, 30            38              46              54
         62            70              78              84          92          130
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Cycle I: CPM (Cyclophosphamide) and 6-TG (Thioguanine). CYCLE II: HY (Hydroxiurea) and DNR (Daunorubicin). CYCLE III: MTX and BCNU (Carmustine). Cycle IV: ARA-C and VCR (Vincristine) same doses settled by LSA_2L_2 POG modified version [23].
For all cycles TIT day 5 and interim maintenance with 6-MP and MTX week 3-8, were given in the same way as described for SR,. Cycles I to IV were repeated twice, from week 30 to 92, after that patients received 6-MP and MTX orally, until week 130. CRT (cranial radiation therapy) was planned as CNS prophylaxis for the HR patients, doses: 1.800 cGy given over two weeks with 1,8 Gy fraction in a linear accelerator through lateral isocentric opposed fields. TIT during maintenance with LSA2-L2 cycles was not done after CRT.

FIGURE 1. Diagram of treatment on the basis of ALL–BFM-90 and LSA_2L_2 protocols. Most chemotherapy agents were used exactly as established by BFM-90 and LSA_2L_2 regimens.[2,23] BFM-90 adjustments are indicated under each phase and briefly summarized in the text. WBC and platelets recovery was required before beginning the next phase. Total duration of treatment was 130 weeks. aa indicates age adjustment; ALL, acute lymphoblastic leukemia; BFM-90, Berlin, Frankfurt, Munster protocol 1.990; CRT, cranial radiation therapy; TIT, triple intrathecal chemotherapy; WBC, white blood cell.

Risk differences, 95% confidence interval (CI), and *P* values were used for comparing this study with the previous study.

RESULTS

Patients' Characteristics

The age of the 123 study patients ranged from 2 months to 16 years (mean 7.6 y, SD 4.4 y) and 61% of the study population were male. Median WBC count and BMF index values at presentation were 14,100/μL (range: 300 to 516,000) and 0.98 (range: 0.42 to 1.94), respectively. Sixty-one percent of the patients were aged 1 to 9 years; 23.6% had a < 0.8 BFM index and 10, 6% > 1.5.

Eighty-five percent of the patients met the HR criteria; however, if they had been classified according to the previous study's risk criteria,[8] then 41% of the present study (n = 51) would have been classified in the SR group and 59% (n = 72) in the HR.

Primary meningeal leukemia was found in 10 children (8.1%), and their characteristics and outcome are briefly summarized as follows. CSF cytology revealed the unequivocal presence of blast cells, WBC count ranging from 34 to 450/μL. WBC peripheral count on diagnosis was higher than 50,000/μL in 6 out of 10 patients; the BFM index was greater than 0.8 in all patients. Three children died from septicemia and bleeding during induction, another 2 from progressive disease, 1 died of pneumonia in CR, 2 died after CNS relapse at 12 and 23 months, and the last 2 were in continuous complete remission (CCR) at 71 and 84 months of follow-up, respectively.

Median follow-up time for the study population was 99 months (range: 54 to 144.6 mo).

Treatment Results

Table 1 shows the study population's characteristics, treatment results, and comparison with the 1987 to 1990 study. PR was good in 72% of the patients, but was

TABLE 1. Comparison of Patients Characteristics and Results of 2 Consecutive ALL Cohorts on the Basis of BFM Therapy

Features/Outcome	1987 to 1990[8] n = 130 (%)	1993 to 1995 n = 123 (%)	Rate Difference (95% CI)	*P*
Age at diagnosis (y)				
< 1	3 (2.3)	5 (4.1)	2% (−7 to 3)	0.52
1-9	87 (66.9)	75 (61)	6% (−7 to 18)	
≥ 10	40 (30.7)	43 (34.9)	−4% (−16 to 7)	
WBC/ $\times 10^9$/L				
< 10	62 (47.6)	54 (43.9)	4% (−8 to 16)	0.545
10-49	35 (26.9)	45 (36.5)	−10% (−21 to 2)	0.099
50-99	6 (4.6)	11 (8.9)	−4% (−11 to 2)	0.169
≥ 100	27 (20.7)	13 (10.6)	10% (1 to 19)	0.040
CNS at diagnosis	9 (6.9)	10 (8.1)	−1% (−8 to 6)	0.90
Mediastinal mass	11 (8.5)	10 (8.1)	0% (−7 to 7)	0.89
PR				
Good	—	81/112 (72)	—	—
Poor	—	31/112 (28)		
Nonevaluable	—	11/123 (8.9)		
Cytogenetics*				
Normal	—	44/123 (35.8)	—	—
Hyperdiploid	—	8/123 (6.5)		
Sample failure	—	37/123 (30.1)		
Standard risk	51 (39.2)	18 (14.6)	—	†
High risk	79 (60.8)	105 (85.4)	—	
Induction				
Death	18/130 (13.8)	9/123 (7.3)	7% (−1 to 14)	0.093
Refused treatment	4/130 (3.1)	2/123 (1.6)	1% (−3 to 6)	0.684
Partial remission (M2)	—	7/112 (6.3)	—	—
Nonresponse (M3)	10/130 (7.7)	5/112 (4.5)	4% (−3 to 10)	0.441
Complete remission	98/130 (75.4)	100/123 (81.3)	−6% (−16 to 4)	0.323
Relapses	43/98 (43.9)	28/100 (28.0)	16% (3 to 28)	0.029
Bone marrow	19/98 (19.4)	18/100 (18.0)	1% (−10 to 12)	0.946
CNS	16/98 (16.3)	6/100 (6.0)	10% (1 to 19)	0.037
Testes	5/98 (5.1)	0	—	—
Combined	3/98 (3.1)	4/100 (4.0)	1% (7 to 5)	1.000
Refused treatment	7/98 (7.1)	3/100 (3.0)	4% (−2 to 10)	0.211
Death in complete remission	5/98 (5.1)	14/100 (14.0)	−9% (−17 to 1)	0.059
Continuous complete remission	43/130 (33.1)	55/123 (44.7)	−12% (−23 to 0)	0.076

*Cytogenetics (study 1993-1995) t1/19 (n = 9/123) 7.3%, t9/22 (n = 6/123) 4.9%, and others (n = 19/123) 15.4%. They are: hazard translocations (n = 7) such as 1/14, 14/19, 14/14, 9/11, 9/14, and 7/Y; T 4/11 (n = 1), in 5 infants it could not identify deletions, hypodiploid, or tetraploid karyotypes (n = 11).

†*P* value noncalculated as different risk criteria were used: only clinical for the first study 1987-1990 (WBC count + age + extramedullary disease) and clinical plus biologic parameters for the 1993-1995 study (age + BFM index + PR + cytogenetics + extramedullary disease).

ALL indicates acute lymphoblastic leukemia; BFM, Berlin, Frankfurt, Munster study; CNS, central nervous system; PR, prednisone response; WBC, white blood cell.

nonevaluated in 11 children, 9 of whom died during induction. Death rate during induction was 7.3% and CR 81.3%. Twelve patients failed to achieve an M1-BM at the end of induction of which 7 were M2 and 5 were M3. Ten of the 12 patients who survived induction but did not achieve CR were poor PR, 4 had more than 100,000/μL WBC on diagnosis, 2 had 9/22 translocation, and 2 were infants, 1 with primary CNS leukemia. Five out of the 7 M2-BM patients achieved an M1-BM after protocol I. However, all died due to early BM relapse (2), myelosupression (2), and progressive CNS disease (2); the remaining 2 patients never achieved a CR and died of progressive disease. The 5 M3-BM children died within 3 months of failing induction due to sepsis and neutropenia.

Eighteen patients relapsed in the BM after achieving CR, 10 within 18 months of CR and the remaining 8 up to 61 months thereafter. All died despite receiving second line chemotherapy. Six children relapsed in the CNS; 3 of them had primary CNS leukemia. Only 1 achieved a second CR, remaining disease-free 3 years later. Four children developed combined relapses; 2 testis/CNS, 1 testis/BM, and 1 skin/CNS. All but 1 died after obtaining a second remission. Seventeen of the 18 patients who relapsed in the BM after achieving CR met HR criteria on diagnosis.

Fourteen patients died during CR; 7 of them while receiving protocol M, 5 due to MTX severe toxicity, and the other 2 from chickenpox-pneumonia and acute bleeding. One death occurred during protocol II and 3 during LSA_2L_2 cycle administration, all being secondary to myelosupression and sepsis. Three patients died during oral maintenance therapy, 2 due to viral pneumonia, and 1 due to CNS thrombosis.

Patients from outside Bogotá suffered a higher mortality rate: 8 during induction, 4 due to MTX toxicity, and 6 during CR, from different causes.

Prophylactic CRT was omitted in 45% of the patients and was administered to 51 of the 76 HR patients and 2 SR who were more than 10 years old. CNS relapse occurred in 3 of 41 nonirradiated patients and in 3 (all with primary CNS leukemia) out of 53 who received CRT (0.75 relative risk; 95% CI 0.16-3.51; Fisher exact test $P = 1.0$).

Figure 2 shows EFS according to base-line risk and PR. The lower panel shows that 10-year EFS was 55% for the good PR patients (95% CI 0.44-0.66) and 24% (95% CI 0.11-0.40) for the poor responders ($P = 0.0008$). The upper panel shows that there was a significant difference in EFS between SR group patients (94%) (95% CI 0.67-0.99) and the HR patients (36%) (95% CI 027-0.45 and $P = 0.0001$).

OS was 58% for good PR, 28% for poor PR, 94% for SR, and 40% for HR patients. Children having a normal or hyperdiploid karyotype had a significantly better EFS (61%) compared with those having t9/22 and t4/11 (14%) ($P = 0.0091$).

Increased CR (81% vs. 75%) and overall (45% vs. 33%) CCR rates (Table 1) were revealed when the results of the present study were compared with those from the previous one carried out at the NCI-BC between the years 1987 and 1990. The earlier study was based on Gatla-Glahem-84, which included: protocol I (induction-intensification), short oral maintenance plus prophylactic CRT for all patients, protocol II (reinduction-reintensification), and long oral maintenance (6-mercaptopurine–MTX) for an overall 3-year treatment.

A statistically significant difference in overall relapse rate (28% vs. 44%, $P = 0.029$) was reported. This difference was mostly due to the reduction in CNS relapses (6% vs. 16.3%, $P = 0.037$). A trend toward improved CCR could also be appreciated; however, even though the death rate in CR was not statistically significant ($P = 0.06$), it was higher in the present study (14% vs. 5.1%). Nevertheless, when results were analyzed according to the year of patient accrual (1993, 1994, and 1995), a progressively decreasing mortality rate was noticed during induction and in CR: 8 patients died during the first year, 6 during the second one, and 4 during the third year. Mortality due to MTX toxicity also decreased (3 patients in 1993, 1 in 1994, and 1 in 1995). A progressive difference was also found for CCR rate (n = 55, 44.7%): it was 39% for 1993 (n = 12 out of 31), 45% for 1994 (n = 19 out 42), and 48% for 1995 (n = 24 out 50).

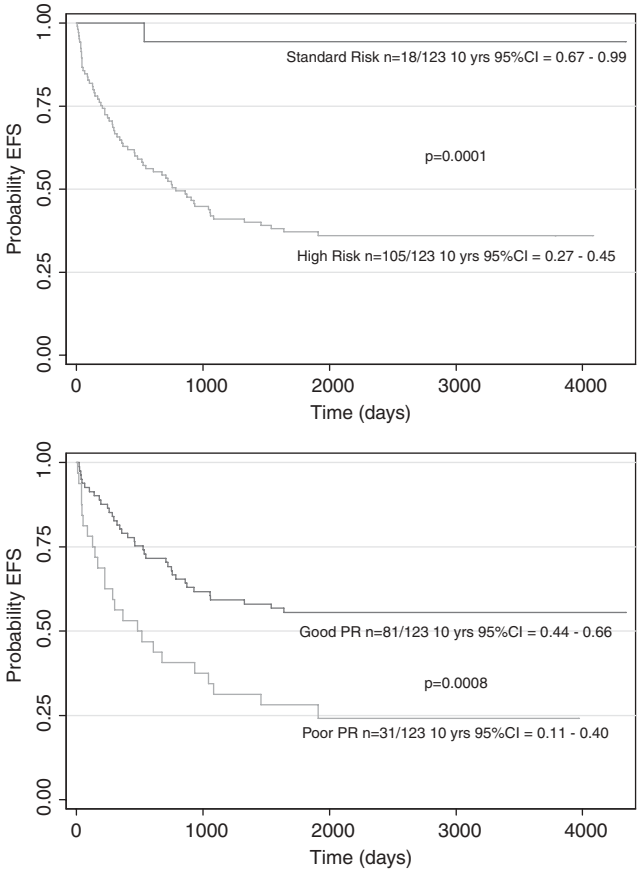

FIGURE 2. Event-free survival by baseline risk (upper panel) and prednisone response (lower panel) at NCI–BC, 1993 to 1995.

Toxicity

Moderate HD-MTX and folinate-rescue at hour 48 were associated with toxicity in 16 patients, classified according to the National Cancer Institute's Common Toxicity Criteria.[4] Five who had been classified as hematologic (IV level) and digestive (III-IV level) died in CR. The remaining 11, classified as hematologic (III-IV level), gastrointestinal (II-III level), or cutaneous (I-II level), improved with supportive care.

Six patients developed hepatitis during chemotherapy: 4 were hepatitis-B surface antigen (HbsAg) positive and 2 had MTX toxicity. Overall, 48 patients were asymptomatic HbsAg carriers. All received interferon and/or antivirals after finishing leukemia therapy. No outcome or toxicity differences were observed between asymptomatic HbsAg carriers and noncarriers ($P = 0.87$). Two patients developed chronic liver disease with portal hypertension; reversible femoral avascular necrosis was seen in 2 other patients.

Memory and learning disabilities not requiring special education were more common among CNS irradiated patients. One reirradiated girl developed hypothyroidism and 1 boy with gonadal relapse, who received testicular irradiation, was reported with hypogonadism. Normal puberty was seen in most patients and growth deceleration and obesity were managed by nutritional counseling. A woman with BM relapse detected 53 months from diagnosis delivered a healthy newborn and subsequently died 21 months later of progressive disease. No secondary malignancies have been reported among the study population.

DISCUSSION

Childhood ALL is a curable disease when treated with intensive chemotherapeutic regimens,[1,5–7,12] such as BFM protocols.[2,3,22]

Our data demonstrated that the outcome for children with ALL treated at the NCI-BC has improved by reducing induction death frequency ($P = 0.093$) and relapse rate ($P = 0.029$). Most of these successes resulted from better chemotherapy regimens, although improved supportive care has also played a role.

In 1993, Colombia had a population of 33,951,168 inhabitants and a childhood mortality rate of 36/1000 children aged < 5 years.[23] Today, the country continues to face social and economic constraints making it difficult to achieve the results obtained in high income countries.

Although induction death and relapse rate were reduced, the results were still far from the 1% and 18% reported by the BFM-90 study group.[2]

Assorted causes can be considered for the differences found when comparing cancer treatment results from LIC and developed countries. Advanced disease conditions were seen in the patients, especially those who came from outside Bogotá, who were suffering systemic life-threatening infections, acute tumor lysis syndrome, or bleeding complications, all requiring intensive pediatric care. There was a need for trained personnel (ie nurses and physicians specializing in pediatric oncology critical care) giving 24 hour attention to patients, which was offered, but in limited conditions. A very low educational level in healthcare was prevalent among family, patients, and caregivers, thereby hampering compliance with compelling cancer therapies because the aforementioned would have preferred "empirical or magical and faster solutions."

The lower relapse rate was mostly due to a more effective CNS preventive therapy, frequency dropping from 16.3% to 6%. Such efficacy was attributed to the combined use of DXM,[17,18,24] long lasting TIT therapy,[7,12–14] and moderate dose MTX infusion.[2,3,6,7,10,11] Prophylactic CRT use was also reduced[7,12,25–27] and only one-third of the HR patients received this type of therapy. The CNS relapse rate had become significantly reduced when compared with previous reports,[28,29] but was still higher than the reported in the BFM-90 study.[2,3,22]

The 5 deaths related to administering moderate dose MTX infusion was a drawback for the survival results; it could likely be attributed to the late use of folinate rescue at hour 48. Furthermore, the greater success subsequently obtained with beginning rescue therapy 36 hours after starting MTX infusion[6] led us to implement it with other measures as follows. Hydration and urinary alkalinization were started 12 hours before MTX infusion and maintained 48 to 72 hours afterwards, carefully checking that urine pH was 7.0, controlling emesis, and omitting prophylactic use of trimethoprim-sulfamethoxazole during MTX infusion.

BM relapses still represent a challenge, as their frequencies were similar in both studies and higher than that reported in BFM-90.[2] Double-delayed intensification[30,31] has already been implemented in an effort to improve on previous results.

Other positive findings concerned the increased CR (81%) and overall CCR rates (45%); however, these results were still inferior to those reported with BFM-90. These improvements were counterbalanced by the failure to achieve CR, the deaths during induction and in CR, and the unexpectedly high BM relapse rate. Further measures aimed at reducing mortality rate should include improving supportive care, particularly concerning the earlier use of intravenous antibiotics for febrile episodes of unexplained pathogenesis in neutropenic patients. These findings demonstrate the delicate balance between intensive chemotherapy and human, social, and financial constraints on managing complications in LIC.

The differences seen in mortality rate and improved CCR in patients enrolled during the first year of the study compared with those enrolled during the second and third years, could be explained by the so-called "learning effect," which certainly reduces therapeutic errors.

Choosing a modified LSA_2L_2 during maintenance for HR patients, rather than the BFM intensive HR blocks, may explain the decreased CCR rate. However, family and children compliance with therapy may have improved—in the outpatient setting—and treatment expenses have also become reduced within an administrative NCI-BC context.

One interesting difference found between the present study (years 1993 to 1995) and the previous one (years 1987 to 1990) was the significantly lower frequency of children having a higher than 100,000/μL WBC count in the most recent study. This significant difference could be explained as evidence of when opportune diagnosis—independently from biologic behavior—shows that progress is being made in educational efforts aimed at general physicians and pediatricians. Technical advances in blood cell count equipment have also allowed fixed WBC counts.

The frequency of poor prognostic factors[32] among our patient population was higher than that reported in the BFM-90 study[2] and most likely contributed toward the inferior results. For instance, 61% of our children were aged 1 to 9 years, 23.6% had a < 0.8 BFM-index, and 8.1% had primary CNS leukemia, contrasting with 80%, 31.6%, and 2.5% in the BFM-90 study, respectively.

Adding biologic parameters, such as PR and cytogenetic information, to the clinical criteria led to implementing a stricter definition of SR patients, as children simply failing to comply with just 1 parameter could then be classified as being HR. This, along with severely ill children being selectively referred to NCI-BC—the main cancer institution in Colombia—explains the large number of HR patients (85%), similar to that reported from El Salvador.[33] However, the stricter definition of risk adopted for the present study resulted in a higher than expected percentage of HR patients being assigned suitable therapy, thereby resulting in an increased CR rate and decreased overall and CNS relapse rates (Table 1). The high frequency of patients achieving only M2 and M3 at the end of induction might have been related to the poor prognostic factors rather than to delayed or incomplete chemotherapy.

PR is an independent prognostic factor,[2,3,34,35] although it cannot identify all patients who subsequently relapse.[35] This simple, low-cost, noninvasive, universally applicable test[1,34,35] obtained results in 90% of our patients. The 28% of poor-PR, a high frequency also reported by European Organization for Research and Treatment of Cancer (18.6%),[36] can be reduced by using TIT therapy on day 1 of induction.[36] Other causes that may have contributed to such high poor-PR rate consisted of reduced compliance with prednisone intake (as only 5-mg tablets were available at the time of the study, thereby requiring many tablets to be taken) and limited experience in performing blast cell count on day 8 (a procedure based on peripheral blood smear lymphocyte-lymphoblast morphology comparison between days 1 and 8).

Karyotype and clone abnormalities were found in 70% of the patients and the incidence of structural abnormalities was similar to that given in previous reports.[9] A better EFS result was obtained for normal or hyperdiploid karyotype, and a poor outcome was once again observed among patients having 9/22 and 4/11 translocations.

One unexpected finding concerned the high frequency of HbsAg carriers, which has also been reported by others.[37] Hepatitis B prevalence in Colombia ranges from 9% to 18%.[38] It is worth noting that blood donors at the NCI-BC are always screened for HbsAg. Transfusion follows the International Red Cross and American Association of Blood Banks' rules and disposable devices are used for chemotherapy administration. Present practice consists of administering recombinant hepatitis B vaccination to seronegative HbsAg patients.[39]

Considering that 61% of the patients were aged 1 to 9 years and 80% had $< 50{,}000/\mu L$ WBC, it is likely that a large proportion of the study patients received more therapy than they would have had in the United States or Canada at that particular time.[40,41]

Our decision to use a therapy formulated on the BFM-90 regimen was based on several considerations. The Children's Cancer Group introduced elements of the BFM into its regimens at the time of the present study,[5,7,12,40] and our previous study has shown better results with BFM than with other alternatives,[8] the institution having had experience with the BFM. This strategy resulted in reduced CNS relapse incidence while avoiding CRT, being administered to 45% of the patients, which was the main purpose of the study.

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REFERENCES

1. Pui CH, Campana D, Evans WE. Childhood acute lymphoblastic leukemia-current status and future perspectives. *Lancet Oncol*. 2001;2:597–607.
2. Schrappe M, Reiter A, Ludwig W-D, et al. Improved outcome in childhood acute lymphoblastic leukemia despite reduced use of anthacyclines and cranial radiotherapy: results of trial ALL-BFM 90. *Blood*. 2000;95:3310–3322.
3. Schrappe M, Reiter A, Zimmermannn M, et al. Long-term results of four consecutive trials in childhood ALL performed by the ALL-BFM study group from 1981 to 1995. *Leukemia*. 2000;14:2205–2222.
4. Poplack D. Acute lymphoblastic leukemia. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 2nd ed. Philadelphia: Lippincott-PhilaRaven; 1993:431–481.
5. Gaynon PS, Steinherz PG, Bleyer WA, et al. Improved therapy for children with acute lymphoblastic leukemia and unfavorable presenting features: a follow-up report of the Children's Cancer Group Study CCG-106. *J Clin Oncol*. 1993;11:2234–2242.
6. Veerman AJP, Hählen K, Van Leeuwen EF, et al. High cure rate with a moderately intensive treatment regimen in non-high risk childhood acute lymphoblastic leukemia: results of protocol ALL VI from the Dutch Childhood Leukemia Study Group. *J Clin Oncol*. 1996;14:911–918.
7. Tubergen DG, Gilchrist GS, O'Brien RT, et al. Improved outcome with delayed intensification for children with acute lymphoblastic leukemia and intermediate presenting features: a Children's Cancer Group Phase III Trial. *J Clin Oncol*. 1993;11:527–537.
8. Buendia MTA, Terselich G, Lozano JM, et al. Acute lymphoblastic leukemia in children: nonrandomized comparison of conventional

vs. intensive-chemotherapy at the National Cancer Institute of Colombia. *Med Pediatr Oncol*. 1997;28:108–116.
9. Pui CH, Crist WM, Look AT. Biology and clinical significance of cytogenetic abnormalities in childhood acute lymphoblastic leukemia. *Blood*. 1990;76:1449–1463.
10. Abromowitch M, Ochs J, Pui CH, et al. High-dose methotrexate improves clinical outcome in children with acute lymphoblastic leukemia: St Jude Total Therapy Study X. *Med Pediatr Oncol*. 1998;16:297–303.
11. Evans WE, Crom WR, Abromowitch M, et al. Clinical pharmacodynamics of high-dose methotrexate in acute lymphocytic leukemia. *N Engl J Med*. 1986;314:471–477.
12. Tubergen DG, Gilchrist GS, O'Brien RT, et al. Prevention of CNS disease in intermediate-risk acute lymphoblastic leukemia: comparison of cranial radiation and intrathecal methotrexate and the importance of systemic therapy: a Children's Cancer Group Report. *J Clin Oncol*. 1993;11:520–526.
13. Pullen J, Boyett J, Shuster J, et al. Extended triple intrathecal chemotherapy trial for prevention of CNS relapse in good-risk and poor risk patients with B-progenitor acute lymphoblastic leukemia: a Pediatric Oncology Group Study. *J Clin Oncol*. 1993;11:839–849.
14. Gelber R, Sallan SE, Cohen H, et al. Central nervous system treatment in childhood acute lymphoblastic leukemia. *Cancer*. 1993;72:261–270.
15. Bennett JM, Catovski D, Daniel MT, et al. Proposals for the classification of the acute leukemias, French-American-British (FAB) Cooperative Group. *Br J Hematol*. 1976;33:451–458.
16. Williams DL, Harris A, Williams KJ, et al. A direct bone marrow chromosome technique for acute lymphoblastic leukemia. *Cancer Genet Cytogenet*. 1984;13:239–246.
17. Jones B, Freeman AI, Shuster JJ, et al. Lower incidence of meningeal leukemia when prednisone is replaced by dexamethasone in the treatment of acute lymphoblastic leukemia. *Med Pediatr Oncol*. 1991;19:269–275.
18. Balis FM, Lester CM, Chrousos GP, et al. Differences in cerebrospinal fluid penetration of corticosteroids: possible relationship to the prevention of meningeal leukemia. *J Clin Oncol*. 1987;5:202–207.
19. Magrath I. Malignant non-Hodgkin's lymphomas in children. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 2nd ed. Philadelphia: Lippincott-PhilaRaven; 1993:537–575.
20. Relling MV, Fairclough D, Ayers D, et al. Patients characteristics associated with high-risk methotrexate concentrations and toxicity. *J Clin Oncol*. 1994;12:1667–1672.
21. Wolfrom C, Hartman R, Fengler R, et al. Randomized comparison of 36-hour intermediate-dose versus 4-hour high-dose methotrexate infusions for remission induction in relapsed childhood acute lymphoblastic leukemia. *J Clin Oncol*. 1993;11:827–833.
22. Reiter A, Schrappe M, Ludwig WD, et al. Intensive ALL-type therapy without local radiotherapy provides a 90% event free survival for children with T-cell lymphoblastic lymphoma: a BFM Group Report. *Blood*. 2000;95:416–421.
23. The World Bank. *The little data book 2006*. WA: Communications Development Incorporated; 2006:65.
24. Gaynon PS, Lustig RH. The use of glucocorticoids in acute lymphoblastic leukaemia of childhood. *J Pediatr Hematol Oncol*. 1995;17:1–12.
25. Nachman J, Sather HN, Cherlow J, et al. Response of children with high risk acute lymphoblastic leukemia treated with and without cranial irradiation: a report from the Children's Cancer Group. *J Clin Oncol*. 1998;16:920–930.
26. Conter V, Schrappe M, Arico M, et al. Role of cranial radiotherapy for children T-cell acute lymphoblastic leukemia with high WBC count and good response to prednisone. *J Clin Oncol*. 1997;15:2786–2791.
27. Conter V, Arico M, Valsecchi C, et al. Extended intrathecal methotrexate may replace cranial irradiation for prevention of CNS relapse in children with intermediate-risk acute lymphoblastic leukemia treated with Berlin-Frankfurt-Munster-based intensive-chemotherapy. *J Clin Oncol*. 1995;13:2497–2502.
28. Steinherz PG. CNS-leukemia: problem of diagnosis, treatment, and outcome. *J Clin Oncol*. 1995;13:310–313.
29. Tubergen DG, Cullen JW, Boyett JM, et al. Blasts in CSF with a normal cell count do not justify alteration of therapy for acute lymphoblastic leukemia in remission: a Children's Cancer Group Study. *J Clin Oncol*. 1994;12:273–278.
30. Nachman JB, Sather HN, Sensel MG, et al. Augmented post-induction therapy for children with high-risk acute lymphoblastic leukemia and a slow response to initial therapy. *N Engl J Med*. 1998;338:1663–1671.
31. Arico M, Valsecchi MG, Conter V, et al. Improved outcome in high-risk childhood acute lymphoblastic leukemia defined by prednisone-poor response treated with double Berlin-Frankfurt-Muenster protocol II. *Blood*. 2002;100:420–426.
32. Smith M, Arthur D, Camitta B, et al. Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. *J Clin Oncol*. 1996;14:18–24.
33. Bonilla M, Moreno N, Neyesa M, et al. Acute lymphoblastic leukemia in a developing country: preliminary results of a nonrandomized clinical trial in El Salvador. *J Pediatr Hematol Oncol*. 2000;22:495–501.
34. Gaynon PS, Desai AA, Bostrom BC, et al. Early response to therapy and outcome in childhood acute lymphoblastic leukemia. *Cancer*. 1997;80:1717–1726.
35. Gajjar A, Ribeiro R, Hancock M, et al. Persistence of circulating blasts after 1 week of multiagent chemotherapy confers a poor prognosis in childhood acute lymphoblastic leukemia. *Blood*. 1995;86:1292–1295.
36. Thyss A, Suciu S, Bertrand Y, et al. Systemic effect of intrathecal methotrexate during the initial phase of treatment of childhood acute lymphoblastic leukemia. *J Clin Oncol*. 1997;15:1824–1830.
37. Locasciulli A, Alberti A, Rossetti F, et al. Acute and chronic hepatitis in childhood leukemia: a Multicentric Study from the Italian Pediatric Cooperative Group for Therapy of Acute Leukemia (AIL-AIEOP). *Med Pediatr Oncol*. 1985;13:203–206.
38. Buitrago B. Patologia geografica: historia natural de las hepatitis B y D en Colombia. *Biomedica*. 1991;11:5–26.
39. American Academy of Pediatrics. Hepatitis B. In: Pickering LK, ed. *Red Book (Libro Rojo). Memoria del Comité de Enfermedades Infecciosas para 2003*. 26a ed. México: Intersistemas; 2004:383–403.
40. Gaynon PS, Trigg ME, Heerema NA, et al. Children's Cancer Group trial in childhood acute lymphoblastic leukemia: 1.983-1.995. *Leukemia*. 2000;14:2223–2233.
41. Maloney KW, Shuster JJ, Murphy S, et al. Long-term results of treatment studies for childhood acute lymphoblastic leukemia: Pediatric Oncology Group Studies from 1986-1994. *Leukemia*. 2000;14:2276–2285.

