Treatment of Childhood Acute Lymphoblastic Leukemia in Central America: A Lower-Middle Income Countries Experience

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Background. Five Asociación de Hemato-Oncología de Centroamérica (AHOPCA) countries have used an adapted BFM-based protocol for childhood acute lymphoblastic leukemia (ALL). Procedure. In the AHOPCA-ALL 2008 protocol, patients were stratified by age, white blood cell count, immunophenotype, central nervous system involvement, day 8 prednisone response, and morphologic bone marrow response to induction therapy. Patients at Standard Risk (SR) received a three-drug induction regimen, a reinduction phase, and maintenance with protracted intrathecal therapy. Those at Intermediate (IR) and High Risk (HR) received, in addition, daunorubicin during induction therapy, a consolidation phase and two or three reinduction phases respectively. Results. From August 2008 through July 2012, 1,313 patients were enrolled: 353 in SR, 548 in IR, 412 in HR. During induction therapy, 3.0% of patients died, 2.7% abandoned treatment, 1.1% had resistant ALL, and 93.2% achieved morphological complete remission (CR). Deaths and abandonment in first CR occurred in 2.7% and in 7.0% of patients, respectively. The relapse rate at a median observation time of 2.1 years was 15.0%. At 3 years, the event-free survival (EFS) and overall survival (OS), with abandonment considered as an event, were 59.4% (SE 1.7) and 68.2% (SE 1.6). Three-year EFS was 68.5% (SE 3.0), 62.1% (SE 2.6), and 47.8% (SE 3.2) for SR, IR, and HR groups. Adolescents had a significantly higher relapse rate (P = 0.001). Conclusions. This experience shows that common international studies are feasible in lower-middle income countries. Toxic deaths, abandonment of treatment, and relapses remain major obstacles to the successful treatment. Alternative treatment strategies may be beneficial. Pediatr Blood Cancer 2014;61:803–809. © 2013 Wiley Periodicals, Inc.

INTRODUCTION

Cooperative projects, developed in the last 20 years through the Monza International School of Pediatric Hematology/Oncology (MISPHO, Monza, Italy) and the International Outreach Program (IOP) of St. Jude Children’s Research Hospital (SJCRH, Memphis), have allowed the growth of many initiatives in Central America [1–4]. Different programs, running separately in single countries of the area, merged in a common organization: Asociación de Hemato-Oncología Pediátrica de Centroamérica (AHOPCA) [5–7]. In this context it has been possible to design and conduct collaborative studies, to institute a prospective clinical registry and to adopt psycho-social care guidelines (derived from the guidelines of the International Society of Paediatric Oncology—SIOP). In particular, since 2008, Costa Rica, El Salvador, Honduras, Nicaragua and Panama have undertaken a cooperative study (AHOPCA-ALL 2008) for treatment of childhood Acute Lymphoblastic Leukemia (ALL) (AHOPCA-ALL 2008) which is based on Berlin–Frankfurt–Münster (BFM) regimens and adapted to the local situation, combining evidence based criteria with feasibility [8]. The aim of this paper is to describe the AHOPCA-ALL 2008 protocol and its preliminary results, focusing attention on the most relevant aspects for Low-Middle Income countries (LMIC), such as toxic deaths and treatment abandonment. Furthermore, subgroup analyses have been conducted with the aim of identifying areas in which improvements can be achieved.

METHODS

The AHOPCA-ALL 2008 study for children and adolescents less than 18 years old with newly diagnosed ALL was approved by ethical committees of all participating centers. Patients were eligible if they had not received previous treatment (steroids could have been given up to 1 mg/kg/day of prednisone for 2 weeks in the last month). From August 1, 2008 to July 31, 2012, 1,365 patients were registered and 1,313 were eligible for the study (25 were not eligible due to previous treatment, 8 received another protocol, and 19 refused treatment) after obtaining informed consent (197 in Costa Rica, 283 in El Salvador, 397 in Honduras, 303 in Nicaragua,
and 133 in Panama). The follow-up was updated at January 31, 2013 (median follow-up time: 2.1 years).

The diagnosis of ALL was established by morphological evaluation of May-Grünwald Giemsa stained smears of bone marrow, combined with cytochemistry (myeloperoxidase negative). In most cases (about 90%), lineage was established on the basis of the immunophenotype determined by flow cytometry. The basic panel included testing for CD19, CD10, Cy CD3, CD13, and CD33 antigens.

Patients were classified in three risk groups: Standard Risk (SR), Intermediate Risk (IR), and High Risk (HR). They were enrolled in HR group if they presented with one of the following: T-cell leukemia/lymphoma, CNS disease (CNS3; <5 leucocytes/µL and blasts in the cytospin of cerebrospinal fluid and/or cranial nerves palsy); testicular infiltration; age < 1 year; prednisone poor response (PPR, i.e., blast count in peripheral blood ≥ 1,000/µL at day −8 after 7 days of prednisone and one intrathecal dose of methotrexate); bone marrow M3 at day +15 or M2/M3 at day +33 of therapy (M2: ≥5% and <25% of blasts in bone marrow; M3: ≥25% of blasts in bone marrow). Translocations (t(9;22), t(4;11), t(1;19)), and hypodiploidy (<45 chromosomes) were additional HR criteria only in Costa Rica, where molecular biology is routinely available. Patients who had none of the previous characteristics were classified in the SR if at diagnosis they were <6 years of age and the white blood cell (WBC) count was <20,000/µL. All other patients were classified in the IR.

**Treatment**

Treatment details and outlines are shown in Supplementary Table SI and Figure S1. Briefly, after the steroid prephase (1 week), a three-drug induction treatment (prednisone, vincristine, l-asparaginase) for SR patients, or four drugs (daunorubicin in addition: two doses for IR and four doses for HR patients), was administered over 4 weeks. IR and HR treatment included a modified BFM consolidation phase Ib, based on cyclophosphamide, 6-mercaptopurine, and IT methotrexate. Protocol III was given one, two, or three times, respectively to SR, IR, or HR groups.

After the first Protocol III, cranial radiotherapy (CRT) was administered to patients in HR group (if older than 2 years): 18 Gy, for CNS involvement and 12 Gy, for prophylaxis in selected subgroups (Supplementary Table SI). Maintenance therapy consisted of daily 6-mercaptopurine (6 MP) and weekly methotrexate given orally, and of vincristine (2 weekly doses) plus dexamethasone (6 mg/m² for 7 days) pulses and IT methotrexate every 8 weeks. Total duration of therapy was 24 months.

Complete remission (CR) was defined by a normocellular bone marrow with <5% leukemic cells and absence of any sign of the primary disease. Disease was defined resistant to treatment if CR was not achieved by the end of phase IB. Missing treatment continuously for more than 6 weeks was counted as treatment abandonment. Relapse was defined as re-occurrence of disease after achievement of CR.

**Protocol Management**

An important role in protocol management was played by the large scale Web application, “Cure4Kids” [9], (www.cure4kids.org) implemented by SJCRH. The site can be used at no charge, by registered users, and allows participants to interact systematically and discuss clinical and therapeutic issues related to protocol application.

**Data Collection and Statistical Analysis**

Demographic and clinical data were registered on a web-based database developed by the IOP at SJCRH, free of charge to every center, named POND (Pediatric Oncology Networked Database, www.POND4Kids.org) [10,11]. POND is available worldwide for registering and studying clinical data. This platform allows the adaptation of forms for data registration and queries of specific protocols. A training on data collection and input was offered to data-managers with on-line weekly meetings during the first 6 months of the study. The local investigators and personnel from the Statistical Office for Paediatric Hemato-Oncology for Low-Income Countries (SOPHOLIC) of the University of Milano-Bicocca regularly reviewed patient data and oversaw the quality of data collection.

For the analysis, overall survival (OS) was defined as the time from the beginning of treatment to death (for any cause) or date of last follow-up. Event-free survival (EFS) was defined as the time from the beginning of treatment until the first event among induction failure (death in induction or resistance at the end of phase Ib), relapse, death in CR, abandonment of treatment, occurrence of a second malignant neoplasm (SMN), or date of last follow-up if no event occurred. The probabilities of OS and EFS were estimated using the Kaplan–Meier method with Greenwood standard error (SE). OS and EFS were estimated for the entire population and by risk group as defined by protocol. A secondary analysis was done censoring patients who abandoned treatment.

We also estimated the crude cumulative incidence of relapse and of death by treatment arm, accounting for competing events, and the OS after relapse, stratifying by time of relapse and site of relapse.

To identify new stratification strategies for patients with unfavorable outcome, a sub-analysis on the IR group was performed, by evaluating the impact of age (<10 vs. ≥10 years) and WBC count (<50,000 vs. ≥50,000) on the cause-specific hazard of relapse in a Cox regression model, stratified by country. Statistical comparisons were made using the log-rank test (for Kaplan–Meier) and Grey’s test (for crude cumulative incidence), and were considered significant when P < 0.05. Statistical analyses were carried out using SAS v9.2 and R software.

**RESULTS**

Demographic and clinical characteristics are summarized in Table I. T-ALL was diagnosed only in 6.2% of patients (5.2% and 9.3% in children less than 10 years or older, respectively). 28.6% were eligible to SR, 43.0% to IR, and 28.4% to HR treatment. However 78 patients were assigned by treating physicians to a treatment arm not consistent with stratification criteria: thus 26.9% in children less than 10 years or older, respectively. 28.6% were eligible to SR, 43.0% to IR, and 28.4% to HR treatment.
Outcome by administered treatment arm is shown in Table II. Forty patients (3.0%) died during induction phase, accounting for 1.4%, 3.3%, and 4.2% of the SR, IR, and HR treatment groups, respectively; 7 died of hemorrhage, 23 of infection, 10 of other causes. Thirty-five patients (2.7%) abandoned treatment in the induction phase (at a median time of 21 days after diagnosis). Among the 50 patients who had M2/M3 bone marrow at the end of phase Ia, 1 died during phase Ib, in 15 patients disease was eventually resistant to treatment (M2/M3 at the end of the phase Ib), while the remaining 34 achieved CR. Thus overall 1,223 patients (93.2%) achieved CR.

Death in first CR occurred in 43 patients (3.3%), accounting for 1.4%, 3.7%, and 4.4% of the SR, IR, and HR treatment groups (30 died of infection, 2 of hemorrhage, and 11 of other causes). Ninety-two patients (7%) abandoned treatment, in first CR (at a median time of 106 days after diagnosis). Relapse occurred in 208 patients (15.0%), most during therapy (in keeping with the limited follow-up) and in the bone marrow. The 3-year cumulative incidence of relapse was 19% (SE 3.0), 24% (SE 2.7), and 37% (SE 3.7) for SR, IR, and HR groups, respectively.

Considering treatment abandon as a failure, 3-year overall EFS and survival were respectively 59.4% (SE 1.7) and 68.2% (SE 1.6) (Fig. 1). By treatment arm, 3-year EFS was 68.5% (SE 3.0), 62.1% (SE 2.6), and 47.8% (SE 3.2) for SR, IR, and HR, respectively (Fig. 2). When patients were censored at the moment of treatment abandon, overall 3-year EFS and survival were 66.6% (SE 1.8) and 76.2% (SE 1.6) (Fig. 3).
74.0% (SE 1.6); 3-year EFS was 77.9% (SE 3.1), 69.3% (SE 2.7), and 53.2% (SE 3.4) for SR, IR, and HR groups, respectively.

There were, however, important overall differences in outcome for the five countries applying protocol AHOPCA ALL-2008, as the 3-year EFS ranged from 47.5% to 73.4%, considering treatment abandon as an event, and from 56.9% to 73.4% when censoring at abandon. Differences among treatment arms remained significant also after adjusting by participating countries, in a Cox model ($P < 0.001$ for EFS with abandon as failure).

**Outcome After Relapse**

The 208 patients who experienced a relapse after front-line treatment had a dismal outcome, with an estimated OS of 23.0% (SE 3.8) at 1 year after relapse. The outcome was different by time of relapse: the 1-year OS in patients relapsing within 18 months from diagnosis was 14.7% (SE 3.8), in those relapsed between 18 and 30 months was 32.2% (SE 8.2) and in those relapsed after 30 months from diagnosis was 55.4% (SE 13.8) ($P < 0.001$). The 1-year OS after relapse was 16.6% (SE 3.8) and 48.1% (SE 10.0) for patients with bone marrow relapse and extra-medullary or combined relapses, respectively ($P < 0.001$).

**Outcome by Age and WBC Count**

Overall 3-year relapse incidence in adolescents (10–17 years of age) was 32.8% (SE 3.4) compared to 18.6% (SE 1.6) in patients less than 10 years of age ($P < 0.001$). When considering the 529 patients with IR features (age ≥6 years and/or WBC ≥20,000/μl and no HR criteria) actually treated with the IR protocol, induction death rate was of 0.6% versus 4.4% in patients ≥1 and <6 years versus ≥6 years; relapse occurred in 48 of 347 patients <10 and in 36 of 182 ≥10 years old; 3-year cumulative incidence of relapse was 17.2% (SE 2.7) versus 28.6% (SE 4.6) ($P = 0.027$) in these two age groups (Fig. 3, panel A). In these same IR ALL patients, the 3-year cumulative incidence of relapse was 20.9% (SE 2.7) and 22.1% (SE 4.7) by level of WBC count <50,000 or ≥50,000, respectively ($P = 0.857$). The difference in outcome by age remained significant also after adjusting for WBC count and gender in a Cox model (hazard ratio of relapse = 1.85, $P = 0.009$) on IR group patients. The same model showed that an higher WBC count at diagnosis was not related to a significant increase in relapse risk ($P = 0.763$). The 3-year cumulative incidence of death in remission induction therapy or in

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**TABLE II. Patients Outcome by Treatment Arm Administered**

<table>
<thead>
<tr>
<th>Events</th>
<th>Standard Risk</th>
<th>Intermediate Risk</th>
<th>High Risk$^a$</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients enrolled</td>
<td>353</td>
<td>548</td>
<td>412</td>
<td>1,313</td>
</tr>
<tr>
<td>Events during remission induction$^b$</td>
<td>16</td>
<td>4.5</td>
<td>27</td>
<td>4.9</td>
</tr>
<tr>
<td>Death</td>
<td>5</td>
<td>1.4</td>
<td>18</td>
<td>3.3</td>
</tr>
<tr>
<td>Abandonment</td>
<td>11</td>
<td>3.1</td>
<td>9</td>
<td>1.6</td>
</tr>
<tr>
<td>Resistant leukemia</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients who achieved complete remission</td>
<td>337</td>
<td>95.5</td>
<td>521</td>
<td>95.1</td>
</tr>
<tr>
<td>Events in complete remission</td>
<td>73</td>
<td>20.7</td>
<td>146</td>
<td>26.7</td>
</tr>
<tr>
<td>Death</td>
<td>5</td>
<td>1.4</td>
<td>20</td>
<td>3.7</td>
</tr>
<tr>
<td>Abandonment</td>
<td>30</td>
<td>8.5</td>
<td>42</td>
<td>7.7</td>
</tr>
<tr>
<td>Second malignant neoplasm</td>
<td>0</td>
<td></td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>Relapse</td>
<td>38</td>
<td>10.8</td>
<td>84</td>
<td>15.3</td>
</tr>
<tr>
<td>Phase of relapse</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During therapy</td>
<td>27</td>
<td>7.7</td>
<td>61</td>
<td>11.1</td>
</tr>
<tr>
<td>After completion of therapy</td>
<td>11</td>
<td>3.1</td>
<td>23</td>
<td>4.2</td>
</tr>
<tr>
<td>Site of relapse</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow</td>
<td>25</td>
<td>65.8</td>
<td>63</td>
<td>75.0</td>
</tr>
<tr>
<td>Extra-medullary</td>
<td>8</td>
<td>21.0</td>
<td>19</td>
<td>22.6</td>
</tr>
<tr>
<td>Bone marrow plus extra-medullary</td>
<td>5</td>
<td>13.2</td>
<td>2</td>
<td>2.4</td>
</tr>
<tr>
<td>Alive in complete remission</td>
<td>261</td>
<td>73.7</td>
<td>365</td>
<td>66.8</td>
</tr>
<tr>
<td>Lost to follow-up after completion of therapy</td>
<td>4</td>
<td>1.1</td>
<td>9</td>
<td>1.6</td>
</tr>
</tbody>
</table>

$^a$ Ninety-six patients received cranial radiation therapy; $^b$ All events for patients at SR or IR occurred in phase Ia. Two deaths and one abandonment occurred in HR patients not in CR at the end of phase Ia; resistance was defined as no CR at the end of phase Ib.

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Fig. 1. Overall survival (OS) and event-free survival (EFS) with abandonment considered as an event.

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complete remission was not different in patients aged <10 or ≥10 years old ($P = 0.301$, Fig. 3, panel B).

**DISCUSSION**

The AHOPCA-ALL 2008 study is a cooperative trial for the treatment of ALL conducted in five different countries in Central America, in the context of a collaborative program with the IOP of SJCRH (Memphis) and the pediatric hemato-oncology center of S. Gerardo Hospital (Monza, Italy). Preliminary results obtained in this study show that AHOPCA-ALL 2008 treatment is feasible also in populations with compromised socio-economic status. It should be considered that these five countries, although defined as middle income countries (GNI per capita between $1,026$ and $12,475$),

![Fig. 2. Event-free survival (EFS, Panel A) and overall survival (OS, Panel B) with abandonment considered as an event by treatment arm: Standard Risk (SR), Intermediate Risk (IR), and High Risk (HR).](image1)

![Fig. 3. Cumulative incidence of relapse (Panel A) and of death in induction phase or complete remission (Panel B) in patients at Intermediate Risk, by age. Two patients <10 years old died at the end of continuation therapy respectively of Varicella pneumonia or meningitis.](image2)
present marked differences. Costa Rica and Panama (upper middle income countries with GNI per capita in 2008 of $6,070 and $6,230, respectively) have a GNI per capita four times higher than Nicaragua or Honduras that are lower-middle income countries ($1,390 and $1,760, respectively in 2008), while the figure in El Salvador is in between ($3,390 in 2008) (data.worldbank.org).

These socio-economic conditions are very likely to have a role in outcome, as already reported [1,12,13] and confirmed indirectly by the abandonment rate (10% overall) in AHOPCA-ALL 2008. Indeed, abandonment was considered a failure in our main analyses, since it is likely associated with a dismal outcome. Interestingly, Costa Rica did not have any case of treatment abandonment; Panama had 2.3% of cases and El Salvador experienced a relatively low rate (4.2%). On the contrary, treatment abandonment was still high in Nicaragua (15.5%) and Honduras (16.4%), compared with the other three countries, despite treatment provided to all patients free of charge. Different strategies have been implemented to reduce abandonment. The most successful have been those based on a closed monitoring of parental information and compliance to schedule appointments by psycho-social workers, and economical support for traveling and basic needs when necessary.

Toxicity could only be estimated as early deaths (3.0%) and deaths in first CR (3.3%) since no data are available on treatment burden. Induction death rates were quite different according to age, being much higher for patients ≥ 6 years old (4.6%) versus patients aged 1–6 years (1.7%), suggesting that a less intensive induction therapy, that is, omission of daunorubicin, might be of benefit for patients < 10 years old at better prognosis.

Causes of death in Induction or in CR are related mostly to infection, which accounts for 64% of all deaths. A major effort is currently ongoing to implement diagnostic and therapeutic strategies aimed to generate epidemiological data on infectious complications. This information, together with a better availability of antibiotics, shall be useful to reduce infectious deaths. Likewise, allowing immediate transfusion of blood products when necessary is important to reduce deaths related to hemorrhage [14].

However, the main cause of treatment failure remains relapse, which, after adjusting for competing events, has an overall incidence of 22.1% at 3 years (SE 1.5); quite high, considering that median follow-up is only 2.1 years. Final outcomes (EFS and Survival) of this study will thus be worse than in this preliminary report due to a persisting risk of any and in particular of extra-medullary relapses.

Current working hypotheses, to improve results, take into account a refinement of risk stratification as well as alternative treatment strategies which may be more suitable for LMIC, provided that they are not associated with an unacceptable burden of toxicity. Consolidation phase IIb was found to be relatively safe, with a death rate less than 1%, and thus it could be extended also to SR ALL patients to improve the current 68.5% 3-year EFS. Alternatively, or in addition, for SR group an intensification of reinduction therapy, that is, protocol III given twice, could be considered too. For IR ALL patients, a clearly worse outcome, due to an excess of relapses, for patients ≥ 10 years old in respect to younger patients, is already demonstrated by the interim analysis. Cumulative incidence of toxic death is similar in these two subgroups (Fig. 3) as well as in patients ≥ 10 years who received the more aggressive HR therapy (3-year 8.3%, SE 3.1). These data suggest that a more intensive treatment can be considered for IR ALL patients ≥ 10 years old. One possibility could be to treat them as the HR group, that is, with four doses of daunorubicin instead of two doses in phase Ia, MTX given at 5 g/m² (instead of 2 g/m²) and Protocol III given three times (instead of twice). However, other alternatives can be considered. The current use of high dose MTX is likely to be sub-optimal since it is given at two or 5 g/m² in infusion over 4 hours and associated with a generous leucovorin rescue because monitoring of serum drug levels is not feasible (five doses of leucovorin are given every 6 hours from hour 36 after infusion of MTX). This generous rescue reduces toxicity, but in turn it may also decrease effectiveness. In fact, as shown by a Scandinavian (NOPHO) study, high doses of leucovorin are associated with higher risk of relapse in pediatric ALL [15]. In addition, shortening the infusion time for high dose MTX reduces the accumulation of MTX in leukemic cells, thus decreasing the antileukemic effect [16]. An ALL-REZ BFM study showed that 1 g/m² MTX by infusion over 36 hours (with two doses of leucovorin rescue given at 15 mg/m² 48 and 52 hours after initiation of the MTX infusion) was as effective as 5 g/m² in 24 hours (with three doses of rescue at 42, 48, and 52 hours after initiation of MTX infusion) [17].

The infusion of MTX 1 g/m² in 36 hours, which does not require the measurement of serum levels of MTX, is not associated with acute renal toxicity, and could be more effective than the current scheme (2 or 5 g/m² in 4 hours) and more suitable for LMIC where assessment of serum levels of MTX was not available.

Another important aspect with a major impact on outcome is compliance with therapy, in particular in adolescent patients. This seems to be a prevalent problem in LMIC [18,19]. It is a rather common experience in fact to observe patients with persistent high blood cell counts during maintenance therapy, suggestive of poor adherence to oral therapy. Interestingly, a Brazilian experience shows that an intermittent regimen for maintenance therapy (6-MP 100 mg/m² given daily for 10 days and 11 days rest, plus MTX 200 mg/m² as 6 hours IV infusion every 3 weeks, with leucovorin rescue 5 mg/m² at hours 36 and 42) is more effective than a continuous regimen (6-MP 75 mg/m² given daily and intramuscular MTX 20 mg/m²/week). This scheme of therapy is reported to reduce hepatic and hematologic toxicity, the need of dose adjustments with minor delays of therapy, transportation costs, and missing school classes by children; thus translating into better treatment adherence [20]. This schedule could be useful to improve outcomes in LMIC.

To improve results the following items are being considered for the next study: psycho-social intervention to reduce abandonment of treatment, the extension of conventional BFM induction therapy to all patients older than 10 years of age, protracted infusion of MTX (1 g/m² over 36 hours) and intermittent maintenance therapy for all patients. In addition it is planned to implement centralized diagnostic cytogenetics and minimal residual disease assessment by flow-cytometry to improve patients stratification. The experience of this cooperative study, with on-line weekly discussions of clinical cases and data entry through internet by trained data-managers, may serve as a model for LMIC, since it allows generation of quality assured data, which may be useful to take evidence-based public health decisions.

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