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REVIEW

Treatment Strategies and Regimens of Graduated Intensity for Childhood Acute Lymphoblastic Leukemia in Low-Income Countries: A Proposal

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Cure rates for children with acute lymphoblastic leukemia (ALL) are 80–85% in high-income countries (HICs) in North America and Western Europe. However, cure rates are much lower in many low-income countries (LICs), where most cases of ALL occur. Over the past several decades partnerships (''twinning'') between HIC and LIC pediatric oncology programs have led to major improvements in outcome for children with ALL in some LICs, often by developing time and resource intensive relationships that allow LIC centers to treat children with regimens similar or identical to those used in HICs. However, the resources are not available in most LICs to allow immediate introduction of intensive ALL treatment regimens similar to those used in HICs. With these thoughts in mind, we present a proposal for a systematic and graduated approach to ALL diagnosis, risk classification, and treatment in LICs. We have based the strategy and the proposed regimens on those developed by the Children's Cancer Group (CCG) and Children's Oncology Group (COG) over the past several decades, beginning with a first level regimen similar to CCG therapy of the early 1980s and then layering on successive treatment intensifications proven effective in randomized clinical trials. Simple monitoring rules are included to help centers decide when they are ready to add new treatment components. This proposal provides a framework that LIC centers can use to provide effective ALL therapy, particularly in regions of the world where few children are currently being cured. Pediatr Blood Cancer 2009;52:559–565. © 2009 Wiley-Liss, Inc.

Key words: ALL; developing countries; leukemia

INTRODUCTION

''Twinning'' programs, whereby a center in a high-income country (HIC) partners with a center in a low-income country (LIC), have led to major advances in childhood cancer care in LICs [1–3]. Treatment of acute lymphoblastic leukemia (ALL) has been a centerpiece of such twinning relationships; prominent examples include linkages between St. Jude Children's Research Hospital (SJCRH) and multiple LICs and links fostered by Monza's International School of Pediatric Hematology-Oncology (MISPHO) and 14 Latin American countries with limited resources [4–6]. Often these efforts have resulted in the use by LICs of ALL treatment regimens similar or identical to those used in Western Europe or North America [7]. This approach makes sense, but to be effective requires significant investment of effort and financial resources by the HIC partner to help the LIC center develop the infrastructure needed to provide such therapy. When these resources are available, this may be the optimal approach. However, such resources are not available to many LICs and other strategies are needed. For example, Karachunskiy et al. [8] reported recently that Russian children with ALL had similar outcomes with the ALL-MB 91 treatment regimen, designed to minimize periods of myelosuppression, and a BFM-90 based regimen, but the ALL-MB 91 regimen had less associated toxicity and required fewer resources. Limited intensity treatment regimens may be even more important as twinning expands to include centers with less developed medical infrastructure, particularly those that do not have a HIC partner. These regimens would be especially useful as a starting point for centers in which few or no children with ALL are cured.

Key issues to consider in the design of ALL treatment regimens for LICs include patient nutritional status, available infrastructure for patient and family support, the health care system and its ability to provide intensive supportive care, the costs of the proposed therapy, and the availability of laboratory tests used in leukemia diagnosis and patient management [9–12].

In HICs there has been a progressive improvement in outcome over time for children with ALL, largely through empirically designed clinical trials that optimized post-induction treatment intensification [13,14]. Frequently, more myelosuppressive therapy has led to decreases in relapse that outweigh any concomitant increases in treatment-related mortality [15–17]. For example, the Children's Cancer Group (CCG) 105 trial conducted in North America in the 1980s showed that delayed intensification (DI) using the BFM protocol 2 chemotherapy blocks led to a significant improvement in outcome for children with intermediate-risk ALL [16,18]. There was a significant increase in toxic death associated with intensive therapy on CCG 105 with an overall treatment related mortality rate of 4.7% on the most intensive arm compared with 1.7% on the least intensive arm. Over time, improvements in supportive care and familiarity with the treatment regimen have led to decreases in the treatment related mortality rate for this therapy in North America. However, the risk-benefit ratio for a specific treatment intensification may be very different in LICs and it is possible that introduction of a DI phase in a LIC center might lead to a substantial increase in toxic deaths and/or abandonment that could negate any potential reduction in relapse risk.

With these thoughts in mind, we present a proposal for a systematic and graduated approach to ALL diagnosis, risk classification, and treatment in LICs. We have based the proposed regimens on those developed by the CCG and Children's Oncology Group (COG) over the past several decades, beginning with a baseline regimen that is derived from that used in the CCG 105 [16] and 106 [15] studies in the 1980s and successively layering treatment intensifications onto this backbone. This baseline regimen

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offers a realistic chance of cure to LIC children with ALL, and is not expected to be associated with excess treatment related mortality in centers that are just beginning to treat ALL patients in an organized manner. A prednisone prophase has been included in all regimens, as it offers the advantage of minimally toxic therapy that can be administered to newly diagnosed patients while optimizing clinical status. The prophase usually results in a gradual decrease in leukemia cell burden, thereby reducing the risk of clinical tumor lysis syndrome, which can be fatal in centers with limited access to dialysis, rasburicase, and intensive care. Furthermore, response to the 7-day prednisone prophase provides critical prognostic information at no cost [13], and gives a 1-week interval to obtain results of more specialized tests such as immunophenotyping prior to initiation of multiagent chemotherapy. Following induction, the lowest levels of therapy can be delivered on an outpatient basis with modest costs. All of the regimens avoid anthracyclines during induction therapy as it is not certain that the benefits outweigh associated risks in LICs. We also avoid high dose methotrexate (MTX), a key component of SJCRH and BFM regimens often used by LICs, due to drug costs, the occurrence of frequent treatment delays due to inpatient hospital bed availability, difficulty monitoring MTX levels in LICs, and increased risks of mucositis and infection in populations with high baseline malnutrition rates.

Each LIC center that elects to follow this approach could intensify treatment by adding components, once it had demonstrated sufficient familiarity and safety with treatment at the prior level. Simple monitoring rules are included, and the entire strategy is contingent on continuous assessment of patient outcomes in real-time, with multidisciplinary discussion of problematic patients and a detailed analysis of all deaths to determine their cause. If excess toxic deaths occur following addition of a specific intensification, then the center could ''step down'' to the prior level until changes are made to overcome these problems. Selection of the initial treatment level at a given center should be based on the rate of toxic death, abandonment, and relapse with the center's current regimen. We envision that LIC centers that do not have significant prior experience in treating ALL and/or those that have a 5-year EFS of less than 50% would begin at Step 1, while those with a 5-year EFS of 50–65% could begin Step 2. More intense levels of therapy should not be considered ''better'' than less intense levels and the step initially chosen is less important than the process of continuous outcome review to determine whether the selected treatment regimen is curing patients in the local setting or is associated with excess death from toxicity. This process is contingent upon the ability of the center to collect accurate clinical and outcome data in a timely fashion for all patients and the ability to analyze these data as needed. Once a center becomes familiar with treatment at the higher levels, they would be encouraged to participate in regional multicenter clinical trials designed by pediatric oncologists in those countries to address specific local problems. An analogous strategy of stepwise implementation of ALL therapy components could be developed based on other HIC treatment protocols; the important point is that the regimen be implemented in a stepwise fashion with frequent assessment of outcomes in the local setting and a logical, data-driven plan for addition or removal of treatment components.

DIAGNOSIS AND CLASSIFICATION

In designing treatment regimens for a LIC, one must first consider what tests are available to diagnose leukemia and to differentiate ALL from acute myeloid leukemia (AML). This can be accomplished with light microscopic examination of bone marrow aspirate or biopsy specimens using standard histochemical stains, along with review of cerebrospinal fluid cytospins. Addition of flow cytometry (performed locally or in regional laboratories [19]) will improve diagnostic accuracy, especially of less common subtypes of ALL and AML (e.g., M0 AML), and distinguish B-precursor from T-cell ALL. Less-expensive, one-laser flow cytometers suffice for these purposes, and, while beyond the scope of the current discussion, could also be used to assess early treatment response via simple algorithms to quantify minimal residual disease [20]. However, we emphasize that there is no compelling need to use flow cytometry to distinguish between B-precursor and T-cell ALL if the pediatric cancer unit is not at a stage where these two entities would receive different therapy.

RISK STRATIFICATION ALGORITHMS AND TREATMENT REGIMENS

We have suggested a simple strategy for risk stratification that divides patients into three groups based primarily on factors that will be readily available in all centers: age, initial white blood cell count (WBC), central nervous system (CNS) status, and early response (Table I). This schema also includes blast cell immunophenotype. If immunophenotype is not available, then patients can be segregated into different groups based only on the clinical factors. At Step 1 (Table I), all patients can receive the same basic treatment (Regimen 1; Fig. 1). Alternatively, cranial irradiation (Regimen 1_{CRT}; Fig. 2) can be added for higher risk and very high risk patients. Strategies for risk stratification and treatment assignment become gradually more complex at Steps 2 and 3.

TABLE I. Risk Stratification Criteria and Treatment

	Lower risk	Higher risk	Very high risk
Definition	B-precursor ALL *and* age 1.00–9.99 years *and* WBC count <50,000/μl *and* prednisone good response *and* CNS 1 or CNS2 *and* Day 15 M1/M2 marrow *and* Day 29 M1 marrow	CNS 1 or CNS2 *and* T-cell ALL *and* WBC <100,000/μl *or* CNS 1 or CNS2 *and* B-precursor ALL with age <1 or >9.99 years *or* WBC count >50,000/μl *and* prednisone good response *and* Day 15 M1/M2 marrow *and* Day 29 M1 marrow	Prednisone poor response *or* CNS3 *or* T-cell ALL *and* WBC >100,000/μl *or* Day 15 M3 marrow *or* Day 29 M2/M3 marrow
Step 1	Regimen 1	Regimen 1 (or 1_{CRT})	Regimen 1 (or 1_{CRT})
Step 2	Regimen 1	Regimen 2	Regimen 2_{CRT}
Step 3	Regimen 2	Regimen 3	Regimen 4

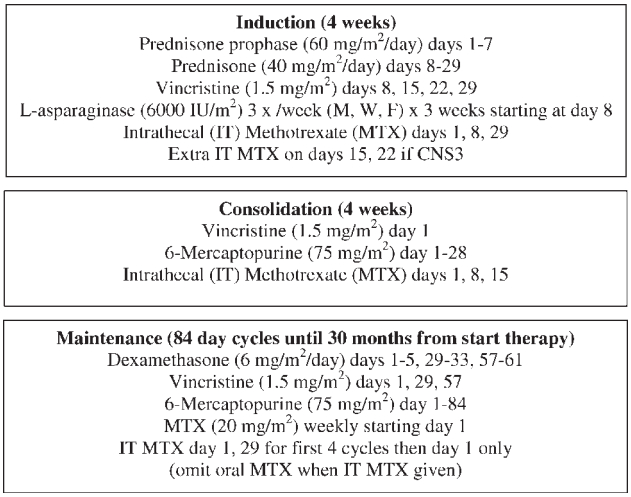

Fig. 1. Regimen 1.

In the following sections, we discuss the details of the different regimens and how they can be integrated successively into the different risk stratification levels. We also provide information on the benefits obtained in HICs when various treatment modifications were tested in randomized clinical trials, and provide simple statistical rules that can be used to monitor outcome following the introduction of treatment intensifications.

Regimen 1: This regimen, which is used for all patients initially, is very similar to the standard arm of the CCG 105 (1983–1989) and 106 (1983–1987) trials [15,16]. In CCG 105, intermediate risk ALL patients [similar but not identical to standard risk (SR) by NCI criteria] were randomized in a 2×2 manner to four different systemic therapies that tested the components of contemporary (at that time) BFM therapy, namely an intensive induction/consolidation [addition of an anthracycline to the three drug induction and intensified consolidation (BFM protocol Ib)], and the addition of a 2-month DI phase analogous to the BFM protocol 2 reinduction/reconsolidation block. Addition of a DI phase improved outcome, but there was no advantage for more intensive induction/consolidation in children with intermediate risk ALL as long as they received a DI [16]. As updated recently, the 16-year EFS for children randomized to a three-drug induction without intensive consolidation or a DI phase was 59% versus 73% for those who received DI [18]. Thus, while addition of a DI phase improved EFS by 14%, 80% of those that were cured with the DI phase could have also been cured with the less intensive regimen.

Based on these data, Regimen 1 utilizes a prednisone prophase, followed by a three-drug induction with prednisone, vincristine, and L-asparaginase. Following completion of induction therapy, no intensive systemic therapy is administered. Regimen 1 makes several changes to the CCG 105 base regimen. First, the prednisone prophase (not given in CCG 105) is at a "standard" dose of 60 mg/m^2, with the prednisone dose dropping to 40 mg/m^2 for the remainder of induction therapy. Second, dexamethasone is administered in Regimen 1 during all phases of post-induction therapy because it proved superior to prednisone in several randomized clinical trials. For example, CCG 1922 randomized NCI SR patients to receive treatment similar to that given in the CCG 105 DI arm with either prednisone 40 mg/m^2 or dexamethasone 6 mg/m^2 given as the steroid throughout treatment [21]. Use of dexamethasone resulted in a significant improvement in outcome, with 6-year EFS of 85% versus 77% ($P = 0.002$). We suspect that the benefit of dexamethasone might be even greater in the absence of a DI phase. Due to concerns about increased infectious morbidity and mortality with dexamethasone, Regimen 1 employs prednisone during induction therapy.

In this and other Regimens, maintenance therapy, consisting of daily oral 6-mercaptopurine, weekly oral (or intramuscular) MTX, and monthly vincristine/steroid pulses, is continued until 2.5 years (30 months) from the date of diagnosis. While vincristine/steroid pulses may not be necessary in the context of modern, intensive therapy, they are likely a key component of less intensive therapies such as those proposed here [22,23]. Arguments certainly could be made for other durations of therapy in the range of 24–36 months, and for different frequencies of vincristine/steroid pulses, but we believe that the proposed duration of therapy and pulse interval are reasonable starting points.

One potential problem that could be encountered with Regimen 1 is inadequate control of CNS leukemia. CCG 105 included a second randomization to extended intrathecal (IT) chemotherapy only versus 1,800 cGy cranial irradiation plus IT chemotherapy for CNS prophylaxis [24]. For patients treated on the intensive therapy arms, both approaches produced excellent CNS control. However, among the patients that received standard systemic therapy without intensive induction/consolidation or DI, there was only an 80% rate of CNS control for those that received IT chemotherapy versus 90% for those that received cranial irradiation ($P < 0.0001$). This difference is one of the major reasons that we propose to use dexamethasone, which gives better CNS control than prednisone [21], post-induction in Regimen 1. However, CNS control might be suboptimal even with dexamethasone pulses during maintenance therapy. While we acknowledge that pediatric cancer units in some LICs might not have access to radiation therapy, we suggest that those centers that do have access to this treatment modality use Regimen 1_{CRT} that includes cranial irradiation for very high risk patients, with an option to also administer Regimen 1_{CRT} to higher

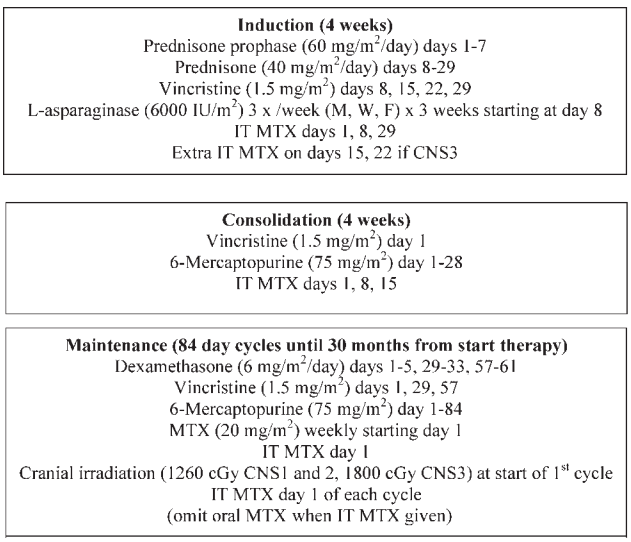

Fig. 2. Regimen 1_{CRT}.

risk patients. To mitigate against excessive toxicity, 1,260 cGy is recommended for patients without evidence of CNS leukemia, and 1,800 cGy for those with initial CNS3 status [25]. While cranial irradiation does have long-term adverse effects, when available it can be delivered in less than 2 weeks, provides excellent CNS control, and is relatively inexpensive.

There are a number of potential advantages and disadvantages to the proposed Regimen 1. Advantages include the fact that this should be an effective ALL regimen, with a low rate of death from toxicity and low cost, which may reduce abandonment. Based on the results of CCG 105 and CCG 106, we expect that Regimen 1 should have anticipated cure rates, in the absence of excess toxic deaths, of about 60% for NCI SR and 40% for NCI high-risk (HR) patients, yielding an overall cure rate of 50–55% [15,16]. Experience with this regimen will allow a pediatric cancer unit in a LIC that is just starting organized ALL therapy to develop infrastructure that will be critical for the use of more intensive therapy. Potential disadvantages include the fact that Regimen 1 will likely cure only about 40% of higher-risk patients, such as those with NCI HR features or T-ALL [15]. We also acknowledge that data are lacking on the efficacy of a prednisone prophase for this treatment backbone, but anticipate that, if anything, the prophase should decrease treatment-related morbidity or mortality.

Given limitations in LICs, we suggest that a reasonable level of treatment expertise should be obtained with Regimen 1 before beginning to intensify therapy. In this setting, we believe that a non-relapse mortality rate in excess of 10–15% during the first 6 months of treatment is unacceptable. Simple rules to assess the rate of non-relapse mortality are provided in Table II. Twenty-five consecutive patients should be enrolled. If there are 1 or fewer non-relapse deaths among these 25 patients, then the upper limit of the confidence interval for the rate of non-relapse mortality is 11.7% and it is reasonable to proceed to the next step. If 2 or more deaths occur among these 25 patients, then a second group of 25 patients should be enrolled. If there are 3 or fewer deaths among these 50 patients, then the upper limit of the confidence interval for the rate of non-relapse mortality is 12.6% at most and it is reasonable to proceed to the next step.

Step 2: Once a treatment center documents safety with Regimen 1, treatment intensifications similar to those commonly used in North American and Western Europe are introduced in a stepwise manner, starting with higher risk patients. Lower risk patients continue to receive the base Regimen 1, while higher risk patients receive Regimen 2 (Fig. 3) and very high risk patients also receive cranial irradiation (Regimen 2_{CRT}; Fig. 4). The key changes in Regimen 2 are administration of 60 mg/m^2 of prednisone during all 4 weeks of induction therapy, and the addition of a 2-month DI phase. The DI phase will improve leukemia control, particularly in the CNS, likely obviating the need for cranial irradiation in most patients. The similarity to contemporary COG therapy for NCI SR patients emphasizes that state of the art care is being provided to patients in LICs. As summarized earlier, addition of a DI phase comes with some risk of increased morbidity and mortality, but improved overall EFS [16,18]. It is very likely that treatment-related mortality will increase when a DI phase is first introduced in a LIC; thus, the toxic death rate during this phase of therapy should be monitored closely using the stopping rules in Table II. If two or more toxic deaths occur among the first 25 patients, then the estimate of the upper limit of the confidence interval for the rate of non-relapse mortality is at least 18.6% and the LIC center should revert to Step 1 while focusing on efforts to improve supportive care.

Step 3: Several major changes occur in Step 3. The lower risk patients now receive Regimen 2 that includes a DI phase and should cure 80–85% of such patients. Higher risk patients receive Regimen 3 that includes a BFM-style consolidation or protocol Ib (Fig. 5). Regimen 3 is very similar to Regimen A of CCG 106, which resulted in a 7-year EFS of 63% for patients with HR ALL [15]. Very high risk patients receive Regimen 4 that includes an intravenous MTX based interim maintenance phase (Fig. 6). The doses used are those that have been tested in CCG 1961 and CCG 1991 and do not include leucovorin rescue, so they can be readily administered without a need for overnight hospitalization. Given the lack of benefit to repeated cycles of post-induction intensification phases for rapid responding patients in CCG 1961 [17] and CCG 1991, we do not favor using repeated cycles of a conventional or reduced intensity DI phase (such as the BFM protocol III) with this backbone. As noted for Step 2, the toxic death rate should be monitored closely using the stopping rules listed in Table II. If excess mortality is encountered with Regimen 3 or 4, then the center should revert to Regimen 2 for all patients while addressing issues related to supportive care.

Once Step 3 has been implemented with non-relapse mortality rates of less than 10–15%, there are a number of interventions that might be considered, such as the use of dexamethasone or anthracyclines during induction, ''augmented'' therapy, or the inclusion of high-dose MTX (at 2 or 5 gm/m^2) for selected subgroups of patients. We believe that the choices of additional intensification are best made by the physicians in LICs; ideally in the context of a clinical trial initiated in the LIC.

PROVISION OF RESOURCES

In order to provide effective ALL treatment in a LIC, mechanisms must be developed to provide the therapy at minimal, and ideally no cost to the patient. To decrease abandonment of therapy, an infrastructure should be developed that can provide food to patients and their families, and provide lodging close to the hospital for families traveling from outlying areas. Most effective twinning programs have focused great efforts on these issues, usually by developing local foundations that raise funds to pay for medications, food, and lodging. Local governments can help by developing mechanisms to pay for medications.

TABLE II. Rules to Assess Regimen Safety

Unacceptable non-relapse mortality rate	First 25 pts (CI, upper limit)	First 50 pts (CI, upper limit)	First 75 (CI, upper limit)	First 100 pts (CI, upper limit)
10–15%	More than 1 death (11.7%)	More than 3 deaths (12.6%)	More than 5 deaths (12.3%)	More than 7 deaths (12%)

CI, denotes the 95% confidence interval.

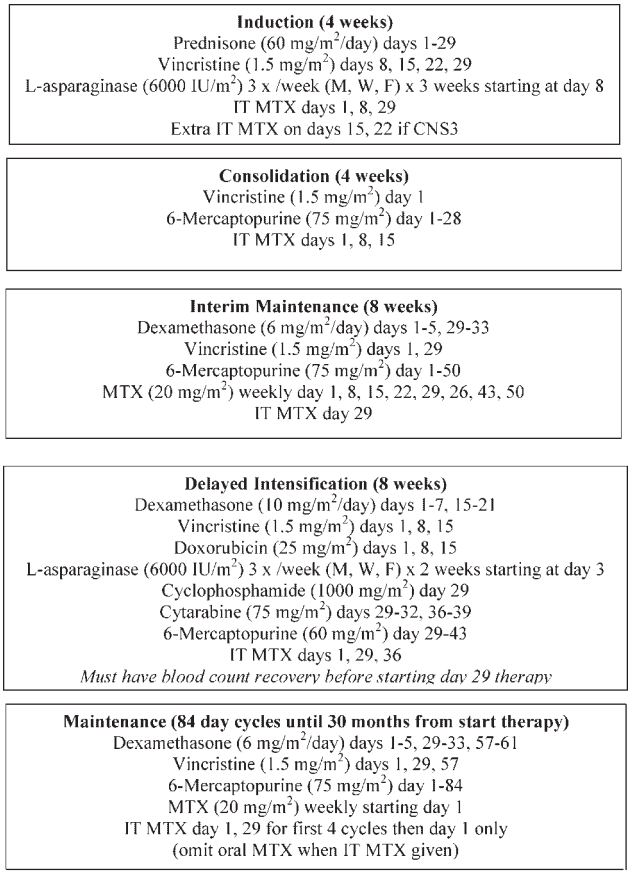

Fig. 3. Regimen 2.

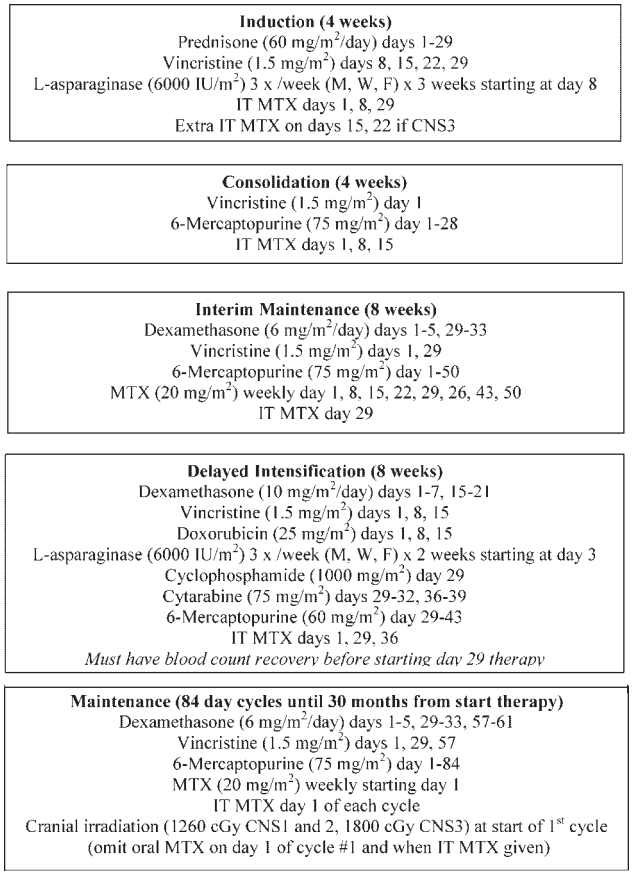

Fig. 4. Regimen 2_{CRT}.

DATA MANAGEMENT PROGRAMS FOR LOW INCOME COUNTRIES

Data Managers

In order to define the optimal treatment strategy in a particular LIC setting, the center must implement uniform, protocol-based care for each ALL patient and carefully monitor rates of toxic death, abandonment of treatment, and relapse [26–28]. Modifications to the chemotherapy regimen can then be made on the basis of periodic review of local outcomes. Success of this approach is critically dependent upon an active data management program comprised of data managers working closely with the clinical team, a database, and data analysis. Data managers in LIC can be hired for as little as US $400 per month in many LICs, and trained with as few as 2 days of on-site training plus ongoing supervision by local doctors and frequent communication via www.cure4kids.org. Regular data manager training sessions in both English and Spanish are held using Cure4Kids, and data managers from any country are welcome to participate at no cost.

Database

Many software tools are available for storage of clinical data. For centers without reliable access to the internet, a spreadsheet may be the simplest solution (available at no cost from www.openoffice.org). Disadvantages of spreadsheets include lack of security, back-ups dependent on the user, and absence of controls over the format of data entered, which can make analysis problematic if dates, diagnoses, and other clinical variables are entered with different formats or alternative spellings. Comparing data with other centers in LICs is also difficult, since it would require merging distinct sets of data. For these reasons, if internet access is available, the pediatric oncology networked database (POND) may be preferable. POND is available at no cost from the International Outreach Program of St. Jude Children's Research Hospital (demonstration and application form available at www.pond4kids.org). This multilingual, secure, online database was designed for data management programs in LICs and is currently used by pediatric oncologists at 43 centers in 28 countries [29,30]. It can store data concerning leukemia subtype, treatment received, toxicity, infectious diseases, nutrition, psychosocial, and socioeconomic status and can be used to measure a variety of outcomes including abandonment, death in remission, event-free survival, and protocol compliance. The ALL treatment regimens proposed here are stored in POND and can automatically generate patient-specific treatment "roadmaps" and calculate drug doses based on the patients weight and height. POND allows sharing of automatically de-identified data with local and international collaborators, hospital administrators, governmental and non-governmental personnel for healthcare planning, outcomes assessment, quality improvement, and research. Control of the data remains with the site administrator, who can activate or deactivate sharing according to the site's needs.

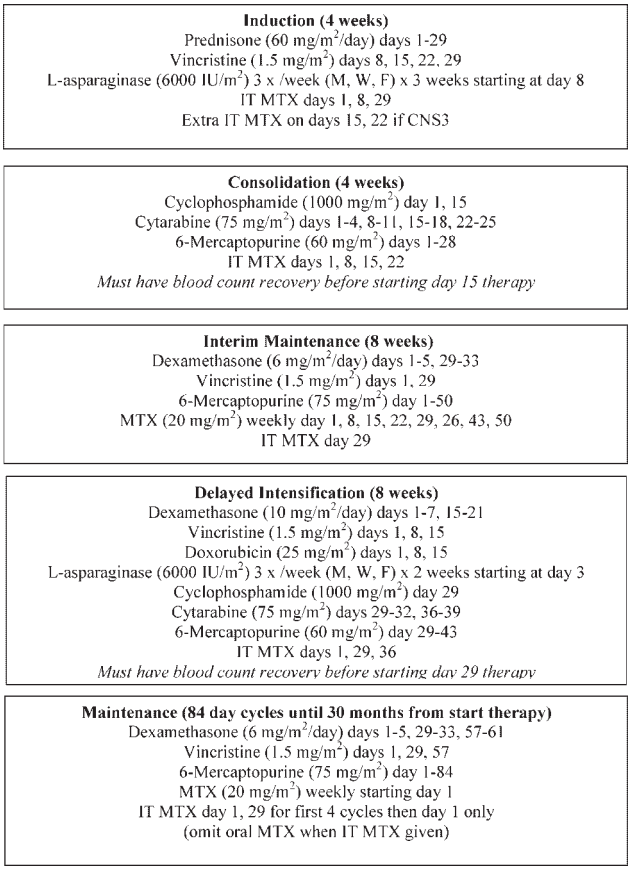

Fig. 5. Regimen 3.

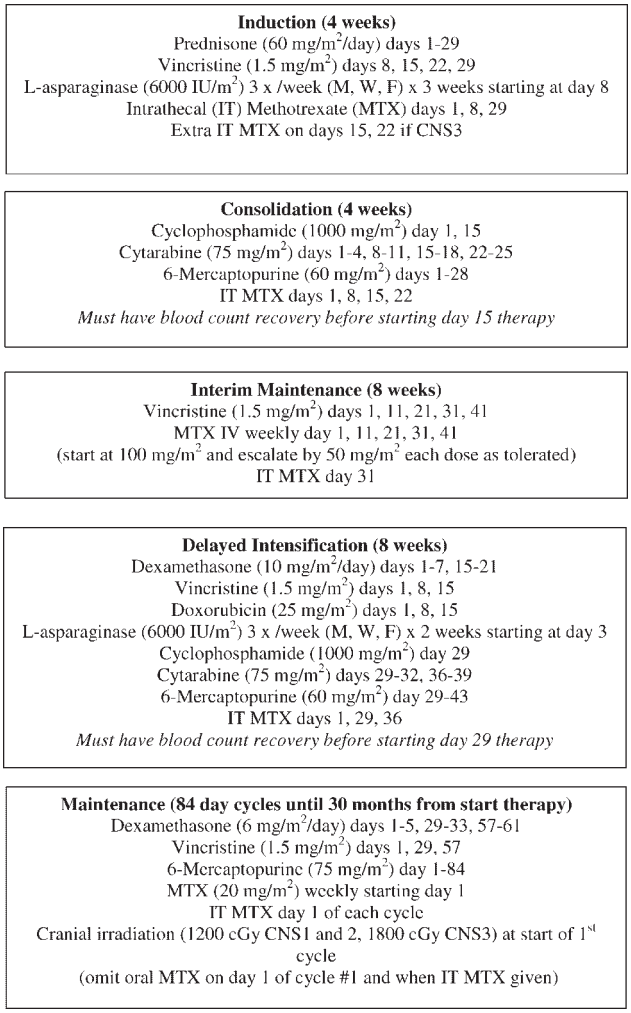

Fig. 6. Regimen 4.

Data Analysis

Although a data manager and database are essential prerequisites, data analysis is required to identify local problems, such as abandonment of treatment, and facilitate development of targeted interventions. While Kaplan–Meier curves can be generated automatically by POND, partnership with a biostatistician with expertise in clinical research is essential. POND version 3 will add the capacity for other statistical analyses, but statistical consultation is needed to take full advantage of these data tools. This remains a problem since many clinicians in LICs do not have access to statistical analysis programs and also lack resources to contract an epidemiologist or statistician to assist with analysis. To overcome this problem, the Monza group has developed a statistical office (Statistical Office Pediatric Hemato-Oncology in Low Income Countries, SOPHOLIC) that collaborates with colleagues in Central America who comprise the Asociación de Hemato-Oncología Centroamericana (AHOPCA) and potentially could advise doctors in other centers.

PARTNERSHIPS BETWEEN LOW INCOME COUNTRY CENTERS

Physicians and their teams that treat children with cancer in LICs face many of the same problems: scarce resources and patients who present not only with cancer, but with extreme poverty, malnutrition, and co-morbid infections. The AHOPCA group exemplifies how partnerships between programs in different countries can benefit all groups. They share treatment protocols implemented via POND that allow rapid assessment of toxicity and event-free survival and the large numbers of patients treated in the AHOPCA centers allows early identification of any problems. Comparison among centers that use the same treatment regimen facilitates identification of problems specific to a single center. We envision a similar collaborative exercise among centers that implement this approach to ALL treatment, allowing colleagues throughout the world to help each other improve care for their patients.

CONCLUSIONS AND PERSPECTIVES

We have presented a framework for treatment of ALL in LICs, with simple monitoring rules that can be used to assess whether the rates of non-relapse mortality are acceptable. We have consciously avoided certain components of therapy used commonly in HICs, such as anthracyclines during induction and high dose MTX. We do not suggest that this is the optimal treatment algorithm, but rather that it represents a reasonable care pathway that should be widely applicable. Centers with no significant prior experience in treating ALL in a comprehensive manner can start with Regimen 1, which

should cure 40–50% of all patients. Centers in other LICs may have already developed the expertise to participate in multicenter trials, such as those conducted by AHOPCA. Many centers may be somewhere in the middle and prepared to start at Step 2 or 3. We hope that this framework will improve care for children with ALL in LICs. Ongoing evaluations will be needed to determine if this is true and introduce necessary refinements.

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