Published in final edited form as:

Expert Rev Hematol. 2014 October ; 7(5): 649–657. doi:10.1586/17474086.2014.949233.

Improving treatment of children with acute lymphoblastic leukemia in developing countries through technology sharing, collaboration, and partnerships

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Summary

Cure rates for pediatric acute lymphoblastic leukemia (ALL) differ markedly in higher- and lower-income countries due to disparate hospital infrastructure and resources. Where means are limited, treatment-related mortality is higher and compliance may be suboptimal. Upfront risk assignment is aimed at “individualizing” therapy according to presenting features in order to avoid over- or under-treatment. However, the necessary technical resources and expertise are not always readily available. We provide suggestions for management of childhood ALL in developing nations. To improve patient care locally, we recommend that communication technology be used to sustain partnerships between sponsoring and partner pediatric oncology programs. The aims of these collaborations should be to prioritize resources, identify existing problems, and reduce treatment intensity and hence treatment-related morbidity and mortality in patients at lower risk of relapse.

Keywords

acute lymphoblastic leukemia; minimal residual disease; risk directed therapy; reduced intensity chemotherapy; lower; mid; higher income countries; sponsor institution; partner institution

Background

Childhood acute lymphoblastic leukemia (ALL) is a curable disease, but in many parts of the world cure remains elusive; access to modern treatment is not uniform, and the early and late complications of therapy are significant causes of morbidity and mortality.

Contemporary treatment outcomes reported by pediatric oncology centers in high-income countries (HIC) indicate that 8 to 9 of every 10 children with ALL are long-term survivors and are considered cured [1]. These startling successes in childhood ALL are associated with (a) the development of pediatric oncology as a subspecialty, (b) the creation of institutions that provide treatment for childhood cancer while simultaneously focusing on biomedical research, and (c) the establishment of national cooperative pediatric oncology groups. A number of successive well designed and stringently analyzed treatment protocols introduced in the early 1970s became building blocks for subsequent therapies [2].

Information from diverse institutions has been shared among investigators who have worked collaboratively to boost cure rates. The approach to the treatment of childhood leukemia has served as a model for the later development and evolution of therapy for childhood solid tumors and adult malignancies.

These notable advances are reported primarily in patients who have access to state-of-the-art treatment in well qualified, well supported institutions located in developed nations; unfortunately, such success is unlikely to be obtained worldwide. Several factors, mainly those associated with needs and availability of resources, explain these disparities [3]. Understandably different public health priorities in HIC vs. low- and mid-income countries (LMIC) result in dissimilar distribution of resources for health care. Moreover, in LMIC hospital infrastructure is usually less well developed, the accuracy and promptness of diagnosis are limited, and modern therapies are less accessible than in HIC. Further, even if treatment can be started, it is often not completed (i.e., treatment is abandoned) for cultural or socioeconomic reasons.

Hence, sociocultural, economic, and medical factors may limit the implementation of new pediatric cancer treatment programs in LMIC. How much of the necessary knowledge and expertise can be transferred to the developing world, where in actuality most children live? How many of the basic resources needed to treat leukemia are available in one nation versus another? What should one focus on first? We will review the experience we have gained by working with physicians who care for less privileged children with leukemia in various geographical areas, and we will offer recommendations for curative therapeutic approaches for these patients. Changes that are easily implemented can greatly improve survival and reduce the toxicity and cost of treatment, in turn allowing more children to benefit.

Curability of ALL

The curability of childhood ALL was established by pioneer trials conducted in the 1960s and 1970s [4]. By current standards, the early trials used what would be characterized as non-intensive treatment. Long-term survivors in these initial trials received limited chemotherapy with not more than 5 basic drugs, including steroids, vinca alkaloids, antimetabolites, and alkylating agents (specifically, prednisone, vincristine, 6-mercaptopurine, methotrexate, and cyclophosphamide). The diagnosis was based on cell morphology, only a few antileukemia agents were available, and there was little knowledge of chemotherapy pharmacokinetics or pharmacodynamics. Since that time, long-term survivors have been monitored to guide the successive refinement of therapy. In retrospect, cures induced by the early approaches occurred primarily among cases that would be classified today as lower-risk ALL. To improve overall outcome, additional drugs were introduced into frontline and maintenance therapy. Predictably, intensification of therapy worsened toxicity. Efforts to reduce the adverse effects of treatment required improvements in supportive care and multidisciplinary approaches, particularly in the treatment and prevention of infections.

The efficacy of increased treatment intensity was tested very carefully, but in a trial-and-error fashion; i.e., a smaller vs. larger number of drugs, half vs. full chemotherapy dosage, and short versus long duration of therapy were assessed in randomized trials. Therapy has

been intensified by the simultaneous use of more agents and/or by higher dosages. As a result, most protocols in worldwide use today, including trials in LMIC, feature intensive initial chemotherapy followed by additional pulses of intensified chemotherapy during remission. As systemic chemotherapy improved with increasing knowledge of pharmacokinetics and pharmacodynamics, changes in central nervous system (CNS)-directed therapy were possible. CNS irradiation was initially viewed as a requisite of curative therapy, but its use has now decreased substantially and in some recent protocols has been eliminated altogether [5], a major achievement considering its carcinogenic potential and adverse effect on the developing brain.

Initial therapy is completed within 3 to 4 months, and then a prolonged phase of maintenance treatment continues for at least 2 years. In general, therapy-related toxicity remains high, schooling is often disrupted, and late effects continue to pose long-term concern. High cure rates in childhood ALL are indisputable, but continuing refinement of treatment is necessary because of its largely empiric, lengthy, potentially toxic, and costly nature.

After ALL was demonstrated to be curable with proper management, the next step was to expand access to as many children as possible. However, the complexity of treatment and its accompanying demands make it difficult to reproduce the cure rates obtained in HIC unless the appropriate infrastructure, training, and conditions are in place. Hence, it is often necessary to adapt treatment protocols to local resources and to lower expectations accordingly.

The challenges of conducting clinical trials in developing countries

It is well established that cure rates among children with ALL differ markedly in HIC and LMIC. For many years, therapeutic breakthroughs have been exported worldwide, in most instances with inferior results. Importantly, not only do cure rates differ, but the causes of treatment failure differ as well. In HIC, reported cure rates exceed 80%, with less than 3% mortality from infection. In contrast, experience has shown that when similarly intensive treatment is delivered in LMIC, early deaths may reach 15% or more because of substandard hospital infrastructure, fewer medical resources, and/or delayed diagnosis and treatment intervention. For example, children with a delayed diagnosis are more likely to present with acute illness, elevated leukocyte count, and infectious and/or bleeding complications. The oncological emergencies that may arise, including impending metabolic, infectious, and/or hemorrhagic complications, require intensive supportive measures. Hyperleukocytosis at diagnosis is associated with early morbidity and mortality related to both microcirculatory leukostasis and hyperviscosity. After remission is induced, other clinical situations may also need immediate attention, particularly when therapy is lengthy, myelotoxic and immunosuppressive. Intensive chemotherapy at different treatment phases may induce prolonged myelosuppression and acute complications, largely of infectious etiology, that require prompt medical intervention. Therefore not only adequate resources but also education and awareness are important. In settings with limited resources, the rate of treatment-related deaths during remission may be 10% or more. Equally important is the

prevention of leukemia relapse, requiring close follow-up to monitor patient tolerance and treatment compliance after complete remission is attained.

How can survival rates improve while resources remain limited? Below we outline several approaches. Importantly, we recommend professional pediatric oncology partnerships between a sponsor institution in a HIC and a partner site in a LMIC help to assess the existing shortfalls in the hospital and community, identify and promote local resources, stimulate discussion, ensure accurate diagnosis, define better treatment delivery, improve laboratory technology to refine leukemia classification, and improve selection of treatment. A good starting point is a thorough analysis of the causes of treatment failure, aimed at reducing the incidence of adverse events by directly addressing the identified problems. To this end, partnerships as mentioned above can be helpful.

Professional partnerships in pediatric oncology

In LMIC, curative therapy may not currently be feasible for all children with ALL, but progress can be made by using available, relatively inexpensive communication technology to strengthen professional collaboration between distant sites. Opportunities include advancing medical education, sharing knowledge, stimulating interest in clinical research, and challenging the treating team to achieve superior results. Sustained partnerships between a sponsor institution in a HIC and a partner institution in a LMIC are effective first steps in developing childhood leukemia protocols that provide up-to-date therapy adjusted to local needs and realities. Professional relationships start with the clear understanding of a collegial, mutually respectful relationship between experts at the sponsor institution and professionals at the partner institution. Senior leukemia specialists may provide consultation in real time to guide diagnosis and treatment and make recommendations, but local attending physicians should retain the responsibility for final treatment decisions. The aim is better patient care that may translate into improved cure rates. The implementation of these programs requires years of persistent effort, including the conduct of periodic web conferences for all new and complex cases, protocol updates, analysis of treatment results, and modification of therapy, if required. In our view, good communication, trust, and availability to resolve problems are instrumental to success. It is also extremely helpful to have written documentation of clinical discussions and to circulate minutes after each live meeting. These minutes contain a wealth of material for review when programs are evaluated. ALL appears to be the model disease to target at the start of an international collaborative program because of its high incidence and potential curability. Moreover, ALL subtypes can be precisely diagnosed with relatively inexpensive and simple technology. Flow cytometry expertise, which is now available in most countries to monitor HIV infection, can be adapted to diagnosis of leukemia and detection of submicroscopic disease, which allow delivery of adapted, more rational and less toxic therapy. This option is an attractive approach in LMIC because it allows less intensive, outpatient chemotherapy for patients at lower risk.

Foundations of good treatment

1) Accurate diagnosis—Correct diagnosis of leukemia is a crucial first step that requires the combined efforts of several specialists. In addition to conventional laboratory tests,

including morphologic examination of bone marrow and cerebrospinal fluid, diagnostic procedures include flow cytometric immunophenotyping. Karyotyping and molecular cytogenetics are important for classification of acute leukemias but are not readily available at all treating institutions. As new diagnostic tools are developed in HIC centers, they may have clinical applications in LMIC as information is conveyed from the sponsor to the partner institutions. Because of the unique biology of Burkitt (mature B-cell) ALL and infant leukemia, these diseases are treated separately.

2) Pediatric oncology units—After the diagnosis is established, we strongly favor the treatment of ALL by pediatric oncologists, preferably using protocol-based therapy. For several reasons, mainly specialized care and infection control, all cases of ALL should be managed in pediatric oncology units.

3) Multidisciplinary teams—The pediatric oncology units should be staffed by skilled multidisciplinary teams and should have 24-hour physician coverage, well equipped clinical laboratories and blood banking, access to intensive care units, and appropriate supplies of chemotherapy agents, antimicrobials, and supportive care medications. Ideally, the multidisciplinary team should comprise pediatric oncologists, pathologists, infectious disease specialists, coagulation experts, radiologists, clinical pharmacists, psychologists, and pediatric oncology nurses. Each specialist has an important role in the treatment of a child with leukemia.

Pediatric oncology nurses in LMIC have limited access to specialized education, which further contributes to the disparity in survival rates between developed and developing countries. To enhance the role of nursing, we have created nurse educator positions at our partner sites to provide continuous pediatric oncology education to nurses with direct patient care responsibilities. Based on our experience, we recommend that sponsor institutions consider this approach, because one nurse educator may train 50 to 75 nurses (6).

4) Close follow-up—Patient progress should be discussed collectively, seeking input from all members of the clinical care team. Documentation of treatment, clinical progress, treatment response, and tolerance of therapy provide helpful data. Detailed medical records facilitate patient care and permit accurate analysis of results. Particularly helpful and feasible interventions include education of patients and families (forthright discussions with parents may be of utmost importance), inpatient delivery of early treatment, guidelines for infection control, and monitoring of treatment adherence, especially in patients receiving oral therapy and in high-risk groups such as adolescents.

Risk stratification

When therapy for childhood ALL was first introduced, the same treatment was delivered to all patients. However, it became evident that responses varied widely despite the same diagnosis and treatment, with some children doing well and others, very poorly. Astute clinical observation and emerging knowledge about the biologic characteristics of lymphoblasts introduced the concept of risk groups, a pivotal model for the design of risk-tailored therapy and a major innovation in the treatment of ALL.

In time the heterogeneity of the disease was unanimously recognized, and treatment has long been adapted according to risk groups to provide rational, tailored therapy. The predictive value of risk factors may vary according to the efficacy of therapy; therefore, classifications constantly evolve. It should be noted that confusion may arise from the use of inconsistent terminology to designate similar patient subsets. Rigorous risk assignment is particularly important in identifying patient cohorts with lower-risk leukemia, a group that will benefit from receiving much less therapy. In LMIC, medical, sociocultural, and economic factors add complexity to the final composition of treatment-related risks.

The significance of minimal residual disease (MRD) determination

Molecular and flow cytometric methods that detect MRD can refine risk groups with much greater sensitivity and precision than morphologic techniques. Biomedical technology currently available in HIC allows the intensity of chemotherapy to be safely reduced for certain subsets of patients. The ability to monitor the submicroscopic response to treatment represents a major breakthrough in tailoring therapy to individual needs. Early treatment response (i.e., MRD level) is the key factor in adjusting treatment in current clinical trials, and the preferred methodology, timing, and interpretation of results have been extensively described. Therefore, the availability of MRD determination greatly facilitates the design of protocols for children with ALL in LMIC [7].

Medical costs can be reduced, as well as outcomes improved, by introducing diagnostic technology that identifies patients whose treatment can safely be de-intensified. In 2006, a simplified and inexpensive flow cytometric assay was developed to extend the benefits of MRD detection to more children with ALL [8]. It identified a subset of patients with excellent final outcome (only 6% risk of relapse), who achieved profound clearance of leukemic cells ($<0.01\%$ leukemic cells among aspirated bone marrow mononuclear cells) after only 2 or 3 weeks of remission induction chemotherapy. The assay was based on the property of exquisite sensitivity of hematogones (expression of CD19, CD10, and CD34 antigens) to glucocorticoids so that only leukemia cells would express this antigen profile during remission induction. When used this antigen profile to monitor MRD levels during early induction treatment, it would identify a distinctive group of very low-risk cases with highly sensitive leukemia (approximately one third of B-lineage ALL cases).

Selection of therapy

Judicious selection of treatment plans is particularly important when resources are limited. Treatment can become prohibitively expensive; in fact, costs are prominent limiting factors. Efforts require a multi-party approach, including government support for pediatric cancer programs, the backing of hospital leadership, and strong alliances with community fund-raisers. It is important to recognize that children with leukemia in LMIC, particularly those living in poverty, often require access to food, lodging, and transportation for the patient and at least one parent. Skilful selection of therapy for each patient is crucial, and it allows the rational distribution of available resources. Although therapy is protocol-specified, it is necessary to adapt it to the unique clinical situation. Experienced physicians with knowledge about the evolution of leukemia therapy can suggest how treatment may be adjusted. There are different approaches to the treatment of childhood ALL, some of which may be equally

effective depending on the circumstances. With this fact in mind, as well as potential toxicity in specific patient subsets, rational adaptation of therapy is a key to improving cure rates.

The Recife trials using MRD

The simplified flow cytometric MRD assay developed at St. Jude provided an opportunity to collaborate with the department of pediatric oncology at the Instituto Materno Infantil de Pernambuco (IMIP) in Recife, in northern Brazil, where ALL patients were experiencing a higher than expected early death rate [9]. The main objectives were to reduce the rate of lethal toxicity and to identify patients with a good early response to induction therapy, whose intensity of treatment could be safely reduced. We focused on this group, reasoning that these children were most likely to be cured. The Recife ALL protocol (RE-ALL-05) opened in 2005, having been designed, implemented, and conducted in close collaboration with St. Jude senior leukemia oncologists. Patients were assigned to a provisional risk group according to their presenting clinical features, blast cell immunophenotype, and molecular genetics. The definitive risk group (and consequent treatment regimen) was determined on day 19 of induction therapy. Patients with negative MRD, defined as $<0.01\%$ leukemic cells among bone marrow mononuclear cells, on day 19 were classified as the low-risk group. Patients with positive day 19 MRD levels were classified as at intermediate risk or high risk. Laboratory tests were performed locally, and MRD determination was supervised by St. Jude experts.

Because of previous problems with early morbidity and mortality, the induction regimen was carefully selected. Patients with low-risk ALL received 4-drug induction with prednisone, vincristine, daunomycin (reduced to 2 doses of 25 mg/m^2), and *E. coli* asparaginase over 4 weeks. Consolidation therapy with high-dose methotrexate (HDMTX, $2.5 \text{ g/m}^2 \times 4$ courses) and leucovorin rescue was given over 8 weeks. Continuation treatment, including one course of reinduction therapy (without anthracyclines), was delivered over 104 weeks. CNS-directed therapy consisted of periodic intrathecal (IT) injections of methotrexate, hydrocortisone, and cytarabine throughout treatment. Patients at intermediate and high risk received more intensive treatment, including 2 additional weeks of induction with cyclophosphamide, 6 MP, and cytarabine. Those at high risk received consolidation therapy with HDMTX $5.0 \text{ g/m}^2 \times 4$ followed by leucovorin rescue. Because serum methotrexate could not be monitored in Recife, patients received HDMTX as inpatients, and leucovorin rescue began 36 hours after initiation of the infusion, earlier than in other protocols. Continuation treatment for those at high risk was administered over 104 weeks and included two courses of reinduction therapy. Because of a higher risk of CNS relapse, IT treatment was intensified and given early during induction therapy for patients with T-ALL. IT therapy was also the main CNS-directed treatment for patients with B- and T-lineage ALL; very few patients received cranial irradiation.

Patient enrollment, presenting features, risk classification, treatment tolerance, and study data updates are reviewed periodically in web conferences by members of the Recife and St. Jude working groups to ensure appropriate protocol documentation, safety, and correct study conduct. Patients who are acutely ill at diagnosis or who are experiencing complications at

any phase of treatment are discussed in detail to decide on appropriate supportive care and chemotherapy adjustments.

The Cairo trial using MRD

Encouraged by the preliminary results obtained in Recife, St. Jude investigators in 2011 helped pediatric oncologists at the Children's Cancer Hospital of Egypt (CCHE) to design and implement a second trial focusing on patients with low-risk ALL. The Egypt low-risk ALL protocol used the same risk model used in Recife; negative MRD ($<0.01\%$) on day 19 of induction indicated low risk of relapse and less intensive therapy. As serum methotrexate could be monitored at CCHE, leucovorin rescue was started 42 hours after the start of the HDMTX infusion, as in most international childhood ALL protocols. At the time this trial was opened, not only was experience accumulating in Recife, but 2 important reports had been published providing evidence of the efficacy and safety of limited therapy for patients with lower-risk ALL [10,11].

Limited therapy for very-low-risk B-lineage ALL

In 2007, a report described the treatment of 653 patients with lesser-risk B-lineage ALL with a 3-drug induction regimen (prednisone, vincristine, and *E coli* asparaginase) followed by antimetabolite therapy. Risk was assigned by clinical features and blast-cell cytogenetics. The 6-year event-free survival (EFS $\pm$ SE) estimate was $86.6\% \pm 1.8\%$ and overall survival was $97.2\% \pm 0.8\%$, without significant late effects. Of note, treatment did not include anthracyclines, alkylating agents, dexamethasone, or radiation [10].

In 2008, the reported 5-year EFS estimate exceeded 97% for non-intensively treated subsets of better-risk B-lineage ALL ($n=261$) monitored by MRD levels on days 8 and 29 of induction therapy. Briefly, induction comprised dexamethasone, vincristine, and *E. Coli* asparaginase and was followed by antimetabolite-based maintenance, steroids/vincristine pulses, and periodic IT MTX [11].

Limited versus intensive treatment for low-risk ALL

The exceptional results described above demonstrate that a proportion of B-lineage ALL patients may be cured without toxic therapy including anthracyclines, alkylating agents, and cranial irradiation, and they support the rationale for lower-risk ALL protocols. We reviewed the results of other international childhood ALL trials published as of 2011, most featuring intensified chemotherapy even for lower-risk groups. We compared the outcomes of subgroups of patients considered to be at low risk, after treatment with intensified chemotherapy vs. more standard, non-intensive therapy. The results are summarized in Table 1, which describes the early systemic therapies, indicating the number of agents given as induction therapy and immediately after complete remission (consolidation phase), and the duration of chemotherapy [12, 13, 14, 15]. Emphasis is on the intensity of early therapy because the period before recovery of normal hematopoietic function is the most critical in patients with leukemia. Most treatment complications occur at this time, as well as the effects of infections the patient may have had at the time of diagnosis. Until bone marrow function is recovered, children require vigilant monitoring by health care professionals and

parents. To ensure promptness of supportive care when needed, inpatient administration of induction therapy may be an option.

By and large, patients with lower-risk ALL had excellent outcomes in these studies, with projected EFS of 85% to 97%, whether treated with more intensive (5-7 induction agents given over 4-8 weeks) or less intensive (induction with 3 drugs administered over 4 weeks) protocols (limited therapy). Long-term results appear quite comparable, further supporting de-escalation of therapy for lower-risk ALL, particularly where resources are limited.

Recent information on limited therapy for MRD-defined low-risk ALL

The results of the British UKALL-2003 trial, reported in 2013, also provide evidence that intensity of therapy may be safely reduced for ALL at low risk of relapse, as defined by MRD. MRD was determined by PCR at the end of induction (day 29). Outstanding results were obtained with reduced therapy consisting of 3-drug induction (dexamethasone, vincristine, and PEG asparaginase), antimetabolite-based maintenance, IT MTX, and one course of delayed intensification. Intravenous high-dose methotrexate as consolidation was not included in the protocol. The 5-year EFS estimate for the 260 treated patients was 94.4%, the relapse rate was 5.6%, and there were no treatment-related deaths. These results were attributed in part to optimum use of steroids and asparaginase. Administration of dexamethasone prior to PEG asparaginase greatly reduced the incidence of hypersensitivity. Importantly, significantly fewer doses and a significantly lower dosage of PEG asparaginase were used in this trial than in other childhood ALL protocols [16]. The treatment approach used in this trial for patients with lower risk ALL was favorably reviewed by experts in the field [17]. However, the UKALL-2003 trial includes anthracycline therapy in the delayed intensification phase and its dosage could be further reduced. These results provide a rationale for reduced treatment intensity for a well-defined and closely followed patient cohort, such as children with ALL highly sensitive to early treatment and enrolled on a clinical trial. Optimal identification of patients with low-risk ALL at the midpoint or end of induction therapy should (a) facilitate the design of simpler, better tolerated treatment protocols, (b) maintain high cure rates, and (c) allow safe administration of strictly tailored treatment.

International cooperative groups

Joining international cooperative groups provides a means of improving outcomes. A recent publication of the intercontinental trial ALL IC-BFM 2002 illustrates the experience of a large international collaborative childhood ALL study group comprising 130 centers in 15 countries. The trial was derived from earlier German and Italian protocols. The overall results were inferior to those achieved by experienced leukemia groups, and treatment results varied among participating countries; however, the investigators concluded that the results had improved within individual countries, which gained from the collective effort [18].

Expert commentary

State-of-the-art risk models for childhood ALL now include **individual response to early therapy**, which offers a major advance in treating childhood leukemia by identifying subsets

of patients with exceptionally good prognosis. It permits more rational selection of therapy, commonly referred to as “risk directed” or, even better, “individualized” therapy. MRD levels are strongly correlated with treatment outcome. Indeed, many studies suggest that MRD is the strongest current predictor of outcome. The development of less complex and costly flow cytometry assays has allowed us to successfully transfer MRD technology to partner sites. Importantly, interpretation of results by St. Jude experts and by local immunopathologists remains highly concordant. Equally encouraging are the ongoing clinical results of the trials in Recife and Cairo. Risk-directed therapy is helping to avoid overtreatment, reduce toxicity, better distribute resources, and reduce patient care costs in LMIC. Moreover, as adverse long-term effects of therapy are reported with increasing frequency in pediatric cancer survivors, efforts to de-escalate treatment whenever possible should be strongly considered [19].

In our view, the collaborative model we have used to transfer expertise, experience, and *knowhow* from our institution to best meet the local needs of our Brazilian and Egyptian colleagues is succeeding beyond initial expectations. To prevent overtreatment of childhood ALL and maximize long-term cost effectiveness, we recommend that sponsoring institutions assist partner institutions in LMIC to develop flow cytometric MRD measurement capabilities. If this goal is met, treatment protocols featuring risk-adapted therapy can be implemented. To pediatric oncologists in LMIC who wish to develop standardized ALL protocols, we recommend the use of limited, non-intensified therapy for patients at lower risk of relapse, based on a) our ongoing trials experience in Recife and Egypt, b) the results described above in patients with low-risk ALL, and c) the absence of any evidence that more intensified chemotherapy regimens produce better results in patients at low risk.

Five-year view

A new generation of refined clinical trials aimed at curing leukemia and decreasing toxicity is being developed at international centers of excellence and will most likely result in cure rates exceeding 90% during the next 5 years. After cure rates are successfully increased, the number of long-term survivors will increase accordingly, and further research will focus on developing less toxic therapies, using chemotherapeutic agents with novel mechanisms of action, and/or introducing different targeted biological therapies developed through gene sequencing studies.

These advances will be transferred to developing nations rather slowly, requiring in the meantime strong professional associations, such as those we describe here, to ensure best possible management of childhood leukemia until continued socioeconomic growth permits better local health care and access to 21st century medicine. Communication technology should improve considerably, with reduced costs, allowing more opportunities for distant medical and scientific interaction.

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Key issues

- Childhood acute lymphoblastic leukemia (ALL) is a curable disease but access to modern treatment is not uniform and early and late therapy-related complications are important causes of morbidity and mortality
- Cure rates among children with ALL differ markedly in HIC and LMIC
- Experience has shown that when intensive chemotherapy protocols developed in centers of excellence are used in LMIC without adjustment to local conditions, early death rates may be prohibitively high
- Once the diagnosis of ALL is established, we strongly favor treatment in a pediatric oncology unit staffed by skilled multidisciplinary teams, preferably using protocol-based therapy
- Current communication technology offers ways to strengthen professional collaboration between sponsor institutions and distant partner sites, creating collegial working groups to discuss patients' presenting features, risk classification, protocol assignment, response to therapy, and overall progress
- Sponsor institutions may facilitate the transfer of biotechnology, i.e., determination of minimal residual disease at key points in treatment, and help introduce ALL protocols featuring risk-adapted therapy
- Patients with ALL at lower risk of relapse may be effectively and safely treated with less intensified protocol-directed chemotherapy, mainly as outpatients, with reduced toxicity and at lower cost
- In our view, the collaborative model used with our Brazilian and Egyptians colleagues to transfer technology, expertise, and *know-how* to best meet the needs of the partner institution is succeeding beyond initial expectations

Table 1

Long-term results of intensive and non-intensive early systemic therapy for patients with low-risk ALL^{*}

Study	No. patients	Induction (Agents, duration)	Consolidation	EFS	Reference
Limited Therapy					
COG 9201	653	Prednisone, vincristine <i>E. Coli</i> asparaginase 4 weeks	MTX 1 g/m ² 24 hr x 6 ^{***} 6-MP, prednisone, vincristine 20 weeks	6-yr 86%	<i>Blood</i> , 2007 Ref 10
COG 9904 ^{**}	261	Dexamethasone Vincristine <i>E. Coli</i> /PEG asparaginase 4 weeks	MTX 1 g/m ² 24 hr ^{***} or MTX 2 g/m ² 4 hr x 6 ^{***} 6-MP, dexamethasone, vincristine 20 weeks	5-yr 97%	<i>Blood</i> , 2008 Ref 11
Intensive therapy					
DFCI 95-01	272	Prednisone, vincristine doxorubicin MTX 4 g/m ² x 1 ^{***} <i>E. Coli</i> or <i>Erwinia</i> asparaginase 25,000 U/m ² 4 weeks	<i>E. Coli</i> or <i>Erwinia</i> asparaginase 25,000 U/m ² /week x 20 20 weeks 6-MP, methotrexate prednisone, vincristine	5-yr 86%	<i>Blood</i> , 2007 Ref 12
BFM 95	758	Prednisone, vincristine daunomycin, <i>E. Coli</i> asparaginase Cyclophosphamide, 6-MP Cytarabine 8 weeks	MTX 5.0 g/m ² x 4 ^{***} 6-MP 8 weeks	6-yr 89%	<i>Blood</i> , 2008 Ref 13
AIEOP 95	115	Prednisone, vincristine <i>E. Coli</i> asparaginase Cyclophosphamide, 6-MP Cytarabine 8 weeks	MTX 2.0 g/m ² x 4 ^{***} 6-MP 8 weeks	10-yr 85%	<i>J Clin Oncol</i> , 2008 Ref 14
Total XV ^{**}	239	MTX 1 g/m ² ^{**} Prednisone, vincristine daunomycin, <i>E. Coli</i> asparaginase Cyclophosphamide, 6-MP Cytarabine 7 weeks	MTX 2.5 g/m ² x 4 ^{***} 6-MP 8 weeks	5-yr 95%	<i>N Engl J Med</i> , 2009 Ref 15

Abbreviations: EFS: event-free-survival; MTX: methotrexate; 6-MP: 6-mercaptopurine

^{*} Although these patients were reported to be at low risk, strict comparison is not possible because of different criteria used for risk stratification.

^{**} Early response to treatment monitored according to MRD level.

^{***} Followed by leucovorin rescue