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Components of Cure: Treatment of Acute Lymphoblastic Leukemia in Indonesia and Other Low-Income Countries

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Protocol-based care for children with acute lymphoblastic leukemia

Cure of acute lymphoblastic leukemia (ALL) requires accurate diagnosis, precise risk stratification, delivery of a complex and prolonged regimen of chemotherapy, and assiduous supportive care. Delivery of this care is best accomplished by following a protocol that lists diagnostic requirements, defines risk categories, specifies chemotherapy drugs, doses, and schedules, and provides guidelines to optimize supportive care. Protocols developed in high-income countries must be adapted to local conditions in low-income countries (LIC) and results frequently assessed to improve care.¹ Development of the protocol document and defining the treatment regimen is only the beginning. Medical and nursing staff must be educated about proper implementation of diagnostic and therapeutic procedures and correct administration of medications. A reliable supply of medications and infrastructure for supportive care must be assured, and patient education materials prepared, reviewed, and disseminated. A suitable medical record system and data management program must be implemented to track therapy administered, outcomes, and compliance. Indeed, implementation of the protocol impacts results far more than the fine points of the regimen itself, and barriers to proper implementation can lead to poor results even when using established treatment regimens. For example, in a cohort of children with ALL in Yogyakarta, Indonesia, treated uniformly with standard chemotherapy, event-free survival was 10% among underprivileged patients and 40% among prosperous patients, largely due to a 47% rate of refusal and abandonment of therapy among the underprivileged versus 2% among the prosperous.²

Importance of compliance

Because the treatment of children with ALL lasts 2 to 3 years and depends largely on oral medications, patients who do not adhere to therapy can dramatically decrease their event-free survival. Much has been published about patient noncompliance.³ In high-income countries, forgetting to administer oral medications is cited by parents as the most common cause of imperfect adherence;⁴ whereas, in LIC financial constraints are the most common reason, and lead to the high rate of abandonment of therapy among underprivileged patients. Education of parents and direct questioning about compliance can improve compliance rates, and should be conducted in a non-judgmental, open-ended way to keep communication open: "How many mercaptopurine pills does your child take each day? When do you give it? Do you give it with food or drink? How many doses were missed in the past week?"

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Role of healthcare providers to implement protocol-based care

In this issue of the journal, Sitaresmi et al. identify noncompliance with the protocol on the part of healthcare providers as another potential cause of treatment failure in childhood ALL. They assessed documentation of high-risk features in the medical record and used questionnaires to gauge healthcare providers' knowledge of criteria to assign patients to the standard- or high-risk treatment arm. They also asked providers about protocol deviations, parental education, and monitoring compliance by asking parents whether and how they administered oral mercaptopurine. In many cases, risk criteria were not documented in the medical record and few doctors or nurses could name all criteria to assign a patient to high-risk status. Of 69 doctors who responded to the survey, 33% reported noncompliance with the protocol for a variety of non-medical reasons. Although the doctors provided reasons of parental non-compliance in a high proportion of patients, including lack of medication (44%), lack of motivation (44%), and lack of financial means (42%), the high rate of physician noncompliance is nevertheless an important finding. Furthermore, only 14% of respondents reported asking parents whether they administer the prescribed medicines and only 7% asked about the dose administered.

Helping healthcare providers who practice in low-income countries

Given the immense clinical workload, lack of opportunities for continuing education, and lack of local mentors for many doctors who treat childhood cancer in LIC, it is not surprising that there are gaps in understanding of the protocol and monitoring patient compliance. What can be done to help healthcare providers in such settings deliver optimal care to their disadvantaged patients? The most important components to facilitate cancer care in low-income countries are listed in the Table. Readers are familiar with the protocol document and data management program, but the third component, frequent communication and review of every patient treated on the protocol has proven invaluable. The case-by-case review can be done online (see Table and Supplemental Figure) and allows networks of clinicians to share experiences and provide consultation to each other. External experts involved in ongoing twinning programs with colleagues in LIC participate as needed to offer advice and moral support. For example, in Latin America, a network of colleagues has joined with collaborators in Europe and North America to develop common protocols, improve nutrition and supportive care, and mobilize resources through twinning programs between centers in low- and high-income countries.⁵ A similar network of collaborators facilitates clinical care and research in Brazil.⁶ Indeed, this method has proven effective all over the globe, including in Indonesia.⁷ Because an adequate data management program and access to experts are taken for granted by many pediatric oncologists in high-income countries, they often focus primarily on development of the protocol document and treatment regimen. This is a mistake in LIC. Proper implementation of the treatment by parents as well as health care providers cannot be ignored because inadequate implementation can reduce event-free survival for ALL from the 80% published in high-income countries to the 20% observed in Indonesia.²

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Howard SC, Ortiz R, Baez LF, et al. Protocol-based treatment for children with cancer in low income countries in Latin America: a report on the recent meetings of the Monza International School of Pediatric Hematology/Oncology (MISPHO)--part II. *Pediatr Blood Cancer*. 2007; 48(4): 486–490. [PubMed: 16883600]
2. Mostert S, Sitaresmi MN, Gundy CM, Sutaryo, Veerman AJ. Influence of socioeconomic status on childhood acute lymphoblastic leukemia treatment in Indonesia. *Pediatrics*. 2006; 118(6):e1600–e1606. [PubMed: 17074838]
3. Pritchard MT, Butow PN, Stevens MM, Duley JA. Understanding medication adherence in pediatric acute lymphoblastic leukemia: a review. *J Pediatr Hematol Oncol*. 2006; 28(12):816–823. [PubMed: 17164651]
4. de Oliveira BM, Viana MB, Zani CL, Romanha AJ. Clinical and laboratory evaluation of compliance in acute lymphoblastic leukaemia. *Arch Dis Child*. 2004; 89(8):785–788. [PubMed: 15269085]
5. Howard SC, Marinoni M, Castillo L, et al. Improving outcomes for children with cancer in low-income countries in Latin America: a report on the recent meetings of the Monza International School of Pediatric Hematology/Oncology (MISPHO)-Part I. *Pediatr Blood Cancer*. 2007; 48(3): 364–369. [PubMed: 16883601]
6. Ribeiro RC, Pui CH. Saving the children--improving childhood cancer treatment in developing countries. *N Engl J Med*. 2005; 352(21):2158–2160. [PubMed: 15917380]
7. Veerman AJ, Sutaryo, Sumadiono. Twinning: a rewarding scenario for development of oncology services in transitional countries. *Pediatr Blood Cancr*. 2005; 45(2):103–106.

Table**Delivery of protocol-based care in low-income countries**

	Components	Purpose	Comments
Protocol document	Eligibility criteria and exclusion criteria; risk classification system	Delineates diagnostic evaluation and risk assignment criteria	A simple checklist eases implementation
	Chemotherapy regimen	Uniform treatment facilitates education of doctors and nurses about patient management and makes outcome assessment meaningful	A treatment roadmap or calendar can be used for parent education and documentation of therapy delivered
	Supportive care guidelines	Recommends supportive care practices that are feasible and effective in the local setting	Outcomes of the recommended practices should be assessed so that recommendations can be adjusted as needed
Data management program	Database	Provides a record of all patients and their outcomes with automatic generation of patient- specific treatment roadmaps. The database should include socioeconomic data.	The Pediatric Oncology Networked Databased (www.POND4Kids.org) is available at no cost and is specifically tailored to childhood cancer
	Data managers	Remove the responsibility for data entry from the doctors	Doctors in low-income countries rarely have extra time to manage data, but must be engaged to review data for quality control
	Data analysis	Identify causes of treatment failure and design interventions to address them	Local, regional, and international collaboration facilitates this process
Case-by- case review	Regular online meetings to discuss each patient	Communication among study centers and with external experts provide patient care advice and point-of-care teaching opportunities	Web conferencing via www.Cure4Kids.org is available at no cost and is used by over 200 groups of healthcare professionals
	Special meetings to review complicated patients	Patient care decisions can be made in real time that have an immediate impact on the individual	This process improves patient outcomes and improves documentation of complications
	Email and phone access to experienced colleagues	Urgent patient care decisions should not be deferred until a regular meeting, but addressed immediately	Volunteers from high-income countries are needed to provide this service to their colleagues in LIC
	Periodic review of adverse events	Careful analysis of patients who have died or abandoned treatment may elucidate preventable causes	