

## Saving the Children — Improving Childhood Cancer Treatment in Developing Countries

Raul C. Ribeiro, M.D., and Ching-Hon Pui, M.D.

Unprecedented gains have been made in the cure rates for childhood cancer during the past four decades. This progress reflects steady improvement in treatment protocols, a multidisciplinary approach to patient care, adequate hospital infrastructure, and psychosocial and economic support for affected families. Perhaps the greatest success has been the 80 percent cure rate among children with acute lymphoblastic leukemia who are treated in a modern center. Most of these survivors have long, productive lives, are well integrated into their communities, and make substantial contributions to society.<sup>1</sup> But this story of medical achievement is tempered by the harsh reality that more than 60 percent of the world's children with cancer have little or no access to effective therapy, and their survival rates are predictably inferior to those in countries with advanced health care systems. The geographic inequality in cancer treatment poses challenges that have only begun to be addressed.<sup>2,3</sup>

Perhaps the most compelling case to be made against investing in better cancer treatment for children in poor countries is that millions of deaths may be prevented by focusing instead on relatively inexpensive strategies for combating infectious diseases. Indeed, the World Health Organization and many international charities have committed their resources to reducing mortality from infectious diseases by two thirds during the next decade. Not surprisingly, noncommunicable diseases and chronic childhood disorders are not among the priorities of these organizations. Although the marshaling of resources to fight infectious diseases clearly has the potential to save the most children in developing countries, we would argue that alternative support mechanisms are also needed to ensure wider access to effective cancer treatment. This argument is not grounded solely in humanitarian considerations; it also addresses the rapidly changing profile of causes of illness and death among children in countries with limited resources.

Although pediatric human immunodeficiency vi-

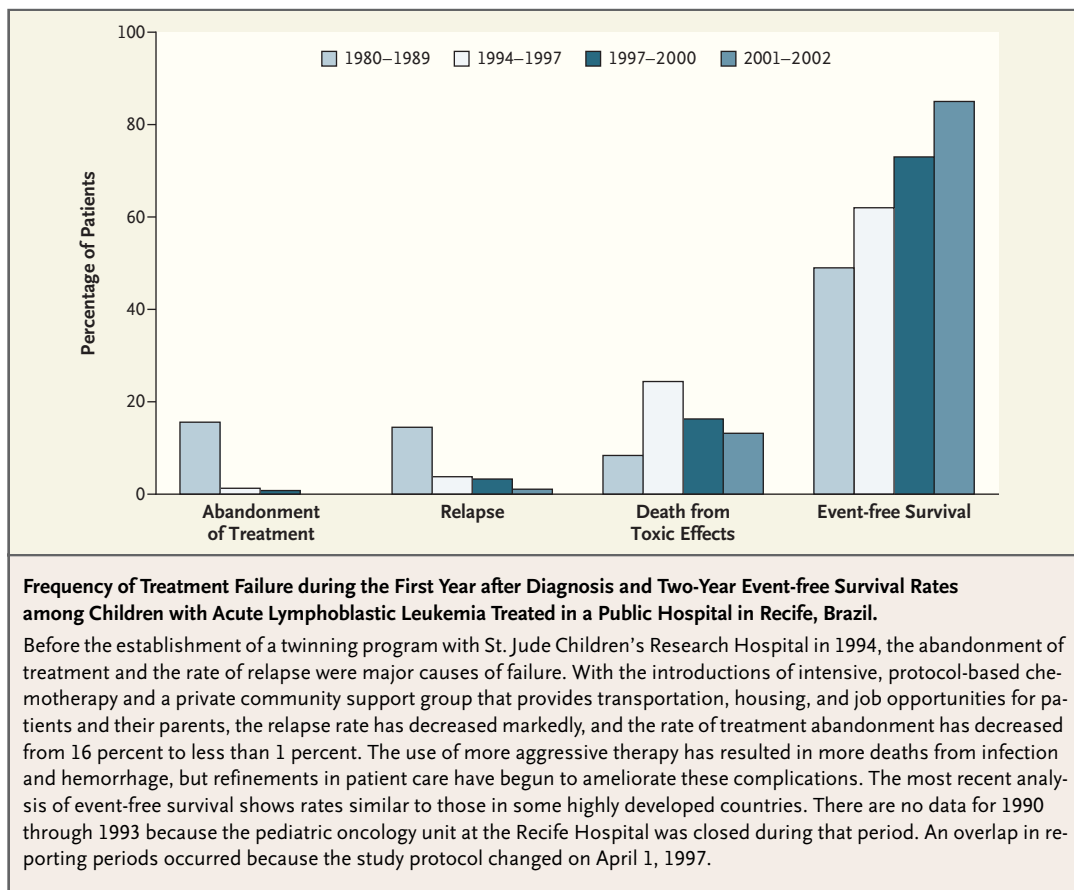
---

Dr. Ribeiro is director of the International Outreach Program and Dr. Pui is director of the Leukemia/Lymphoma Division at St. Jude Children's Research Hospital in Memphis, Tenn. Dr. Pui is also a clinical research professor at the American Cancer Society.

rus infection and AIDS remain a critical health priority in sub-Saharan Africa, cancer is emerging as a major cause of childhood death in developing regions of Asia, South and Central America, northwest Africa, and the Middle East, as a result of reduced mortality from preventable infectious diseases.<sup>3</sup> For example, in 1960, the rate of death among infants in China was 150 per 1000 live births; among children under five years of age, the death rate was 225 per 1000 live births. By 2002, the rates had decreased to 31 per 1000 and 39 per 1000, respectively. As the population of Chinese children nears 300 million, a conservative projection of 45,000 new cases of pediatric cancer each year can be made.

At the Shanghai Children's Medical Center, which serves the only Chinese city in which health insurance for catastrophic diseases is offered, 234 children with acute lymphoblastic leukemia were admitted for treatment between October 1998 and June 2003. According to Dr. J.Y. Tang of the medical center, therapy for 66 of these children (most of whom did not live in Shanghai) had to be abandoned, apparently for financial reasons, and another 52 children died of leukemia or treatment-related complications, leaving only 116 in continuous complete remission. This problem is much worse elsewhere in the country, especially in rural areas: only about 10 percent of Chinese children under 14 years of age who have acute leukemia receive protocol-based therapy, according to Dr. L.J. Gu, also of the Shanghai center.

What, if anything, can be done to bring the benefits of modern cancer treatment to more children? The most immediate and substantial results will probably come from expanded access to treatment, the elimination of reasons for abandoning treatment, and better control of complications of infections. Possible approaches to achieving these goals are admirably covered in the recent book *Cancer in Developing Countries: The Great Challenge for Oncology in the 21st Century*. One strategy, described in the chapters by Masera et al. and Cavalli, emphasizes a partnership ("twinning") between institutions in developed countries and those in underdeveloped countries, an approach that seems most likely to have long-term success.



Examples of the twinning approach to childhood cancer treatment have been in place in Central and South America, northwest Africa, and southeast Asia for as long as 10 years.<sup>3,4</sup> These programs have reduced the rates of abandonment of treatment, relapse, and death due to toxic effects of treatment (see graph), and the investments they have attracted have led to improvements in access to treatment and hospital infrastructure.

Briefly, twinning fosters interactions between public hospitals in developing countries and established cancer treatment centers, with the goal of improving survival rates among children with cancer. The best results have been obtained when local oncologists were recruited as program directors and asked to promote the idea of a strong pediatric oncology unit among their peers and coordinate the training of providers. Although at first the partner institution in the more affluent country may subsidize the costs of treatment, these and other expenses are eventually met with funds raised by charitable groups in the community. Such alliances have generated sufficient momentum to allow some hospitals in Central and South America to begin sharing

their expertise with other oncologists in the developing regions of Latin America, by developing joint treatment protocols and consulting about problems in the management of childhood cancer.

Can twinning be effective in countries that lack even rudimentary health care systems? We believe that a low level of development does not pose an insurmountable obstacle to a productive partnership. In parts of Africa, for example, it may be possible to cure children of Burkitt's lymphoma by treating them with cyclophosphamide alone, and there is evidence from Malawi that even a simplified twinning program can save lives.<sup>5</sup> Thus, a modified program concentrating on education, training, and the treatment of the most responsive cancers could be quite effective.

Most progress in pediatric cancer treatment has been stimulated by research involving children in Western countries. Since the susceptibility to and pathogenesis of cancer are heavily influenced by genetic background, environmental exposure, and lifestyle, we must broaden research to include cases in developing countries. It will be easier to do so if the development of pediatric-cancer units in poor



Courtesy of Dr. J.Y. Tang.

**A Patient with Acute Lymphoblastic Leukemia at the Shanghai Children's Medical Center.**

countries leads to the evolution of international banks of cells and tissue and of cancer registries that collect long-term follow-up data.

It has been said that if we are to preserve civilization, we must make certain its benefits are available to the many, not reserved for the few. The de-

velopment of curative treatment for children with cancer is a benchmark for medical progress, and such treatment must not be sequestered within the borders of a few countries. The strategy we describe is only a start, but it could ignite a spirit of achievement that may ultimately reach even the least privileged nations.

*Cancer in Developing Countries: The Great Challenge for Oncology in the 21st Century*, edited by S. Tanneberger, F. Cavalli, and F. Pannuti, was published by Zuckschwerdt, Munich, 2004.

1. Pui CH, Cheng C, Leung W, et al. Extended follow-up of long-term survivors of childhood acute lymphoblastic leukemia. *N Engl J Med* 2003;349:640-9. [Erratum, *N Engl J Med* 2003;349:1299.]
2. Pui CH, Schrappe M, Masera G, et al. Ponte di Legno Working Group: statement on the right of children with leukemia to have full access to essential treatment and report on the Sixth International Childhood Acute Lymphoblastic Leukemia Workshop. *Leukemia* 2004;18:1043-53.
3. Pui CH, Ribeiro RC. International collaboration on childhood leukemia. *Int J Hematol* 2003;78:383-9.
4. Howard SC, Pedrosa M, Lins M, et al. Establishment of a pediatric oncology program and outcomes of childhood acute lymphoblastic leukemia in a resource-poor area. *JAMA* 2004;291:2471-5.
5. Kazembe P, Hesselning PB, Griffin BE, Lampert I, Wessels G. Long term survival of children with Burkitt lymphoma in Malawi after cyclophosphamide monotherapy. *Med Pediatr Oncol* 2003; 40:23-5.

## Gag Clauses in Clinical-Trial Agreements

Robert Steinbrook, M.D.

Related article, page 2202

Gag clauses in clinical-trial agreements prevent investigators from examining the data independently or submitting a manuscript for publication without first obtaining the consent of the sponsor. Sponsors with a financial interest in the outcome of clinical research can suppress negative results. They can also interfere with the publication of unfavorable data on safety, as it was recently alleged that Merck officials did in the company-sponsored "Advantage" study of rofecoxib for the treatment of osteoarthritis published in 2003.<sup>1</sup> Some of the hidden data, like those related to cyclooxygenase-2 inhibitors and the use of antidepressants in children, may eventually become public, but other studies are never reported.

In 2001, the International Committee of Medical Journal Editors (ICMJE), which then represented 11 general medical journals, including the *New England Journal of Medicine*, began to require that the respon-

sible author of a study state in writing that he or she accepted full responsibility for the conduct of the trial, had access to the data, and controlled the decision to publish.<sup>2</sup> Subsequently, researchers at Duke University (Durham, N.C.) surveyed the provisions in clinical-trial agreements between medical schools and industry sponsors and found that "academic institutions routinely engage in industry-sponsored research that fails to adhere to ICMJE guidelines regarding trial design, access to data, and publication rights."<sup>3</sup> In response, the researchers and others proposed that there should be standard contract provisions for industry-sponsored research conducted at academic medical centers.<sup>4</sup>

In 2005, has anything changed? The short answer is no. Dr. Robert M. Califf, the director of the Duke Clinical Research Institute, noted recently, "I do not see any evidence that the average contract of a site participating in a multicenter study is any better now than when we wrote the article." According to Dr. Steven E. Nissen, the director of the Cleve-

Dr. Steinbrook is a national correspondent for the *Journal*.