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Commentary

Strategies to improve outcomes of children with cancer in low-income countries

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1. Feasibility of curing children with cancer in low-income countries

The feasibility of curing children with cancer has been demonstrated primarily in resource-rich countries. The 80% cure rate for childhood acute lymphoblastic leukemia (ALL) in these developed countries only serves to underscore the poor survival rates in resource-poor areas such as India, where the per capita gross domestic product (GDP) in 2003 was only US $2538 and where 80% of the population lives on $2 per day or less. With a current population of about a billion people, including 340 000 000 (33%) children younger than 15 years, an estimated 8160 cases of childhood ALL occur per year in India. Treatment for ALL is long and costly and places significant economic burdens on both the family and the healthcare system. Given the glacial pace of economic growth in many developing countries, what are the options for parents and doctors who wish to bring curative therapies to children in such regions?

Demonstration that cure is possible in select cases is the first step toward mobilizing resources in developing countries to improve paediatric cancer care on a national scale. This first step usually results from a twinning program, in which a center in a resource-rich country forms a partnership with a center in a developing country [1,2]. In this issue, Magrath *et al.* [3] report the data of two decades of hard work and careful research that has resulted from a twinning relationship between the US National Cancer Institute and three centers in India. They demonstrate that in India, 40–60% of selected children with ALL can be cured when treated in a paediatric oncology center of excellence on an affordable protocol that has manageable toxicity [4]. This finding should motivate India's public, government, and non-governmental organizations to devote resources to the care of children with ALL. In developing countries, treatment for ALL and other curable illnesses is justified and should be considered a fundamental right of children [5,6].

2. Practical aspects of treating children with cancer in low-income countries

The improvement in outcomes reported by Magrath and coworkers were attributable to uniform protocol treatment in well-organized paediatric cancer units with data management infrastructure, access to expert consultants, and continuous quality improvement efforts. As a result, 60% of children with ALL treated at the Tata Memorial Hospital (in Mumbai, formerly Bombay), and 41–43% of those treated at the All India Institute of Medical Sciences (New Delhi) and the Cancer Institute of Chennai (formerly Madras) were cured. These measures did not depend on unavailable or expensive technologies and could feasibly be replicated throughout the country. As centers of excellence develop within India, they will serve as points of origin for further expansion of paediatric oncology services and expertise, so that eventually a strong national program

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can be developed and sustained. The table illustrates the phases of such a process, which can begin with a single pilot project to demonstrate that childhood cancer can be cured in some cases. Such a pilot project in Malawi led to cure of 33–64% of children with Burkitt lymphoma using a simplified protocol [7,8] (see Table 1).

Comparison of outcomes obtained at three paediatric cancer units provides additional insight into how to address local problems. Why was the 4-year event-free survival almost 20% higher at the Tata Memorial Hospital, when all 3 centers had well-trained physicians, saw many patients with ALL each year, and used the same treatment protocol? At the All India Institute of Medical Sciences, the rate of death caused by toxicity was 22.8%, more than double the 10.6% rate at Tata Memorial Hospital; at the Cancer Institute, the 41.1% relapse rate was more than 10% higher than those at the other two centers. At least some of these disparities can be explained by differences in the patients treated. At the Cancer Institute, a surprising 43.1% of patients had T-cell ALL, compared to 20.7% in Mumbai, and the median age and number of patients with white blood cell counts greater than 100×10^9/L were also significantly higher. A more detailed study of the causes and timing of toxicity-related death and relapse that is adjusted for presenting features will be needed to identify specific aspects of healthcare delivery that could be improved in each center.

The importance of paediatric cancer units and centers of excellence must not be underestimated. In Sao Paulo, Brazil, where the annual per capita GDP is $5838, the government and private insurers pay for the majority of paediatric oncology care. Children with ALL are treated at many medical centers that compete for patients. However, despite the relatively prosperous economy of São Paulo, the 5-year rate for childhood ALL in that city in 1998 was only 41% because of the lack of centralized paediatric oncology care [9]. By contrast, in several centers of excellence in São Paulo, Campinas, Recife, and other Brazilian cities, where most paediatric oncology care occurs in paediatric cancer units, the 5-year event-free survival has been consistently above 60% [10]. In Recife, for example, it has increased from 32% to 63%, despite a mean per capita GDP of only $1049 [11]. This result supports our contention that outcomes are improved when resources are concentrated in dedicated paediatric cancer units and those units are developed into centers of excellence.

Another successful model of the development of specialized paediatric cancer units is the national paediatric oncology program in Chile, the *Programa Infantil Nacional de Drogas Antineoplásicas* (PINDA). The Chilean government, which funds paediatric cancer care, insists that patients receive diagnosis and initial care in a certified paediatric cancer unit with follow-up and other supportive services offered by satellite clinics closer to patients' homes [12]. A national paediatric oncology program can provide the intellectual and organizational framework for development of a national ALL protocol. The protocol should include a minimally toxic remission induction regimen that incorporates a prephase with prednisone for patients who have malnutrition or infection at diagnosis, or who are at high risk of tumor lysis syndrome. Patients should be kept in or near the hospital during intensive phases of therapy, and there should be frequent patient and family educational sessions about febrile neutropenia and other signs of potentially life-threatening infection. The use of hematopoietic growth factors during treatment of childhood ALL is not recommended in resource-rich countries and certainly is not indicated in developing countries, where other healthcare expenditures have higher priority. Conservative use of prophylactic platelet and packed red blood cell transfusion is advisable everywhere, but transfusion use should be even more conservative in developing countries, where the safety of the blood supply may be uncertain. In this regard, platelet transfusion is seldom necessary during remission induction that includes prednisone and asparaginase because patients are generally in a hypercoagulable state [13].

A national ALL protocol should include drugs that are readily available and as inexpensive as possible, so that the program will be sustainable in the long term [14]. A contingency plan that includes recommendations for chemotherapy substitution should be explicitly stated in the protocol to anticipate temporary shortages of particular drugs. The occurrence of a drug shortage that necessitates chemotherapy substitution should be documented in the patient's medical record, the research database, and the hospital's administrative records. In Central America, several countries recently experienced shortages of mercaptopurine and all-*trans*-retinoic acid. Colleagues in neighboring countries were able to ship a supply by bus to the affected centers so that the patients' therapy need not be interrupted. While such collegiality is admirable and desirable, a contingency plan for therapeutic substitution remains essential in developing countries.

Development of a national paediatric oncology program and a national ALL protocol is only the first step. Oncologists, referring physicians, nurses, pharmacists, and other members of the healthcare team must be educated regularly about the treatment regimen, the expected toxicities, supportive care guidelines, and contingency plans. Agarwal *et al.* [15] have already made substantial progress in this regard. In addition, the data management infrastructure must be in place to ensure the possibility of continuous quality improvement. Any deaths should be reviewed to identify aspects of the healthcare system that could be improved. In fact, commitment to continuous real-time review of significant adverse events should be a prerequisite to participation in the protocol. Such review can be facilitated

Table 1
Steps to implementation of a National Paediatric Oncology Program in low-income countries

Phase	Purpose	Requirements	Role of outsiders	Example
Pilot project	A successful pilot project demonstrates that childhood cancer can be cured in the local setting	A dedicated leader and a twinning relationship with a center of excellence in resource-rich country	Complete technical and financial support	Lilongwe Central Hospital, Malawi [7,8]
Paediatric cancer unit	Centralizes resources devoted to the treatment of childhood cancer to improve efficiency and the quality of care	Cooperation of a variety of paediatric specialists and support of the hospital administration	Major technical and financial support	La Mascota Children's Hospital, Managua, Nicaragua [1]
Center of excellence	Development of the paediatric cancer unit into a center of excellence	Mobilization of patients, parents, the government, and non-governmental organizations	Modest technical and financial support	Instituto Materno Infantil de Pernambuco, Recife, Brazil [11]
Satellite centers	Extend the benefits to a wider geographical area and reduce the burden of travel on families from distant areas	Training and supervision of satellite-center personnel by the center of excellence with increased governmental support	Modest technical and financial support	Hospital Materno-Infantil, Tegucigalpa, Honduras [16]
Regional program	Increased quality of care and independence of centers of excellence and satellite centers with coverage of a wide geographic area (province, state, or adjacent small countries)	The regional government takes responsibility for treatment of all children with cancer as a regional priority	Minor technical and financial support	AHOPCA, Central America
National program	Nationwide network of centers of excellence and satellite centers. National paediatric oncology association for protocol design, continuing education, and advocacy activities	The national government takes responsibility for treatment of all children with cancer as a national priority	Advisory only	PINDA, Chile [12]

PINDA, Programa Infantil Nacional de Drogas Antineoplásicas.
AHOPCA, Asociación de Hematología-Oncología Pediátrica Centroamericana.

by conducting online conferences and establishing workgroups using tools available without cost at www.cure4kids.org.

To investigate the feasibility of treatment on a modern ALL protocol in select centers in India, Magrath and colleagues appropriately limited eligibility to patients able to remain close to the treatment center during the period of remission induction and consolidation therapy. Only 4% of these patients abandoned therapy, a rate much lower than the 24% reported in Honduras [11,16]. Now that success has been documented for select patients in select centers, the program can be extended to patients who live at a greater distance and to additional paediatric cancer centers. This extension will require specific intervention to prevent abandonment of treatment, which is the most common cause of ALL treatment failure in developing countries [11,16]. The most successful measures to prevent abandonment include low-cost (or free) housing for patients who live at a distance, economic support (meals, basic food staples, transportation vouchers, contact with local community agencies), patient/family education, satellite clinics, social worker intervention within 24 h of any missed appointment, and parent support groups. Medical non-compliance represents a milder form of the abandonment problem, in which patients continue to attend clinic, but receive only a portion of the planned treatment. This problem can be minimized by provision of subsidised medications, patient and family education, parent support groups, and frequent monitoring of compliance (open-ended questioning about medications taken, monitoring for inappropriately high blood counts, and measurement of thioguanine levels in patients prescribed mercaptopurine).

Magrath and colleagues are to be congratulated for their persistence in implementing a modern ALL protocol in several paediatric cancer centers in India. This work provides the foundation for further improvement of outcomes that can be accomplished by reducing death from toxicity and extending the benefits of protocol-based care to additional centers and patients.

Conflict of interest statement

None declared.

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References

1. Masera G, Baez F, Biondi A, *et al*. North-South twinning in paediatric haemato-oncology: the La Mascota programme, Nicaragua. *Lancet* 1998, **352**(9144), 1923–1926.
2. Pui CH, Ribeiro RC. International collaboration on childhood leukemia. *Int J Hematol* 2003, **78**(5), 383–389.
3. Magrath I, Santa V, Advani S, *et al*. Treatment of acute lymphoblastic leukaemia in countries with limited resources; lessons from use of a single protocol in India over a twenty year period. *Eur J Cancer* 2005, **41**(11), 1570–1583.
4. Shanta V, Maitreyan V, Sagar TG, *et al*. Prognostic variables and survival in paediatric acute lymphoblastic leukemias: cancer institute experience. *Pediatr Hematol Oncol* 1996, **13**(3), 205–216.
5. Tognoni G, Masera G, Pui CH, *et al*. Statement by members of the Ponte di Legno group on the right of children with leukemia to have full access to essential treatment for acute lymphoblastic leukemia. *Ann Oncol* 2005, **16**(1), 169–170.
6. 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**, 1043–1053.
7. Kazembe P, Hesseling PB, Griffin BE, *et al*. Long term survival of children with Burkitt lymphoma in Malawi after cyclophosphamide monotherapy. *Med Pediatr Oncol* 2003, **40**(1), 23–25.
8. Hesseling P, Broadhead R, Mansvelt E, *et al*. The 2000 Burkitt lymphoma trial in Malawi. *Pediatr Blood Cancer* 2005, **44**(3), 245–250.
9. Mirra AP, Oliveira Latorre M, Veneziano DB, editors. Incidence, mortality and survival of childhood cancer in São Paulo. Ministry of Health, National Cancer Institute of Brazil, 2004
10. Brandalise S, Odone V, Pereira W, *et al*. Treatment results of three consecutive Brazilian cooperative childhood ALL protocols: GBTLI-80, GBTLI-82 and -85. ALL Brazilian Group. *Leukemia* 1993, **7**(Suppl 2), S142–S145.
11. Howard SC, Pedrosa M, Lins M, *et al*. Establishment of a paediatric oncology program and outcomes of childhood acute lymphoblastic leukemia in a resource-poor area. *JAMA* 2004, **291**(20), 2471–2475.
12. Campbell M, Salgado C, Quintana J, *et al*. Improved outcome for acute lymphoblastic leukemia in children of a developing country: results of the Chilean National Trial PINDA 87. *Med Pediatr Oncol* 1999, **33**(2), 88–94.
13. Howard SC, Gajjar A, Ribeiro RC, *et al*. Safety of lumbar puncture for children with acute lymphoblastic leukemia and thrombocytopenia. *JAMA* 2000, **284**(17), 2222–2224.
14. Barr RD, Sala A, Wiernikowski J, *et al*. A formulary for paediatric oncology in developing countries. *Pediatr Blood Cancer*., Epub 3/11/2005.
15. Agarwal BR, Marwaha RK, Kurkure PA, *et al*. Indian National Training Project Practical Paediatric Oncology (INTPPPO): 2nd National Teacher's Meeting, Consensus Report. *Med Pediatr Oncol* 2002, **39**(4), 251
16. Metzger ML, Howard SC, Fu LC, *et al*. Outcome of childhood acute lymphoblastic leukaemia in resource-poor countries. *Lancet* 2003, **362**(9385), 706–708.