Establishment of a Pediatric Oncology Program and Outcomes of Childhood Acute Lymphoblastic Leukemia in a Resource-Poor Area

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A CUTE LYMPHOBLASTIC LEUKEMIA (ALL), the most common childhood cancer, has a cure rate of 80% in resource-rich countries.1-6 However, more than 80% of the world’s children live in less-advantaged countries, where the cure rate generally does not exceed 35%.7-11 The outcome of treatment of childhood ALL, which depends on effective chemotherapy and supportive care, serves as an index of the status of pediatric oncology in countries with limited resources. Because of its high incidence and its curability, ALL is a logical initial target for pediatric cancer programs under development in such countries. The causes of treatment failure in resource-poor countries include relapse, abandonment of therapy, and death from toxicity because of suboptimal supportive care, delayed diagnosis, and comorbid conditions.8-19 Strategies to reduce some of these problems have been studied,17,18 and establishment of a dedicated pediatric oncology program in El Salvador was associated with an increase in ALL survival from 5% to 48%.9

Context  The cure rate for childhood acute lymphoblastic leukemia (ALL) differs markedly between developed and developing countries.

Objective To assess the effect of a multidisciplinary team approach and protocol-based therapy on the event-free survival of children with ALL in an area with limited resources.

Design, Population, and Setting A retrospective cohort study at a pediatric hospital in the resource-poor city of Recife, Brazil. We reviewed medical records of the outcomes of 375 children with ALL diagnosed between 1980 and 2002. Eighty-three children were diagnosed in the early period (1980-1989), in the absence of a dedicated pediatric oncology unit, protocol-based therapy, specially trained nurses, 24-hour on-site physician coverage, and ready access to intensive care. Seventy-eight children were treated (all according to protocol) during the middle period (July 1994 to March 1997). During the recent period (April 1997 to December 2002), 214 children were treated with protocol in a dedicated pediatric oncology unit staffed 24 hours by pediatric oncologists and oncology nurses. Improvements were implemented gradually during the middle period and were completed during the recent period.

Main Outcome Measure Event-free survival was estimated by the Kaplan-Meier method. Events included death from toxicity, disease progression or relapse, and abandonment of treatment.

Results The 5-year event-free survival improved steadily: 32% (95% CI, 21%-43%) in the early period, 47% (95% CI, 36%-58%) in the middle period, and 63% (95% CI, 55%-71%) in the recent period. The probability of cause-specific treatment failure in the early, middle, and late periods, respectively, within 1 year of diagnosis was 14% vs 3.8% vs 3.3% for relapse; 6.0% vs 12% vs 9.8% for death from infection; 2.4% vs 13% vs 4.2% for death from noninfectious toxicity; and 16% vs 1.3% vs 0.5% for abandonment of therapy.

Conclusion Treatment of childhood ALL in a dedicated pediatric oncology unit using a comprehensive multidisciplinary team approach, protocol-based therapy, and local support and funding is associated with improved outcomes in a resource-poor area.

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In the 1980s, there was no dedicated pediatric oncology program in Recife, the capital city of the Pernambuco province of northeast Brazil, where the mean annual per capita income is only US $1049. During the past 15 years, systematic improvements have been made in all aspects of pediatric oncology care, despite little change in the

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region’s economy and rate of infant mortality (85 per 1000 live births in 1991 vs 74 in 2000). We describe the effect of the changes in the pediatric oncology program on the estimated probability of event-free survival of children with ALL.

**METHODS**

**Study Population**

We reviewed the medical records of outcomes of 375 children with ALL diagnosed between 1980 and 2002 in Recife, Brazil. During the early period (1980-1989), patients were treated at the Barao Lucena Hospital, a public general pediatric hospital with no pediatric oncology unit, protocol-based therapy, consistent supply of medications, specially trained nurses, or 24-hour physician coverage and little access to intensive care. In 1990, the pediatric oncology service was closed until July 1994, when a pediatric oncology service was opened in the Instituto Materno Infantil de Pernambuco. During the middle period (July 1994 to March 1997), children with ALL were treated with the St Jude Total XI protocol but were cared for in the general wards by nurses who had no specialized oncology training.

During the recent period (April 1997 to December 2002), patients were treated according to the St Jude Total XIIIB protocol in a dedicated pediatric oncology unit staffed continuously by pediatric oncologists and oncology nurses and had rapid access to intensive care.

TABLE I summarizes the major changes in the pediatric oncology service. Most improvements were initiated during the middle period and fully implemented during the recent period. From 1994 to 2000, 28 to 32 children per year with...
newly diagnosed ALL were treated in the Instituto Materno Infantil de Pernambuco; after expansion and renovation of the hospital, the number of referrals increased to 45 in 2001 and 46 in 2002. Because Pernambuco has a population of 2.6 million children younger than 16 years and the incidence of ALL is 32 per 100000 per year, 83 new cases of childhood ALL per year would have been expected in the province.

This study was approved by the ethics committee of the Instituto Materno Infantil de Pernambuco, and the research was conducted in accordance with the Declaration of Helsinki.

Sources of Support and Costs

Many improvements in care were supported by the Núcleo de Apoio à Criança com Cáncer (NACC, The Childhood Cancer Support Center), a local nonprofit, nongovernmental foundation established to support the needs of children with cancer. The foundation raises funds in the private sector to assist families with lodging, transportation, vocational training, medical costs not covered by the hospital, and other needs. In addition, NACC has developed and sustained parental support groups and implemented a tracking system so that patients who miss clinic visits can be contacted within 24 hours to prevent missed therapy. NACC also provides work opportunities to parents who do not reside locally. Family members can make candy and baked goods, and the profits can be used for their support during their child’s treatment. The annual budget of the pediatric oncology unit is US $1 436 000, including all medical care and psychosocial support; the average cost to treat a child with ALL is US $16 700 a year. The government provides 50% of these funds, NACC 45%, and St Jude 5%.

Diagnosis of ALL and Statistical Analysis

The diagnosis of ALL was made by morphologic and cytochemical evaluation of aspirated bone marrow. Patients aged 1 to 10 years at diagnosis and with a white blood cell count less than 25 000/µL, no mediastinal mass, and no leukemic infiltration of the central nervous system were considered to have standard-risk leukemia; all others were considered to have high-risk leukemia. The probability of event-free survival was estimated by the method of Kaplan and Meier; the estimates were compared by using the log rank test. Adverse events were defined as death from toxicity, disease progression or relapse, development of a second cancer, and abandonment of treatment before completion of chemotherapy, defined as missing 6 or more consecutive weeks of treatment and follow-up. A multivariable Cox proportional hazards model was used to evaluate the effect of treatment period, high-risk vs standard-risk leukemia, and sex on the risk of treatment failure. The probability of treatment failure during the first year after diagnosis was calculated for each cause and each period. Only treatment failure during the first year was considered in this comparison to avoid bias caused by different follow-up times in the 3 periods.

RESULTS

Patients were a median age of 5.4 years (range, 0.1 to 17.2 years); 201 were boys, and 168 had standard-risk ALL. No significant differences were observed between the treatment periods in patient characteristics (TABLE 2). Eighty-three children were diagnosed during the early period, 78 during the middle period, and 214 during the recent period. The 5-year event-free survival estimate was 32% (95% confidence interval [CI], 21%-43%) for the early period, 47% (95% CI, 36%-58%) for the middle period, and 63% (95% CI, 55%-71%) for the recent period (FIGURE). The 5-year event-free survival estimate was significantly higher for the early period than for the middle (P = .005) and recent (P < .001) periods. The hazard ratios for treatment failure were 2.4 (95% CI, 1.5-3.8) for early vs recent period, 1.8 (95% CI, 1.1-3.1) for middle vs recent period, 1.7 (95% CI, 1.2-2.4) for high-risk vs standard-risk ALL, and 0.9 (95% CI, 0.6-1.2) for male vs female sex. TABLE 3 lists the cumulative incidence of cause-specific treatment failure within 1 year of diagnosis for the different periods.

COMMENT

Treatment failure in the early period was caused by relapse disease, abandonment of therapy, and death from infection or hemorrhage. The high rate of relapse resulted from the absence of standardized therapy and the unreliable supply of medications. The use of uniform protocol-based therapy and a reliable supply of medications in the middle period reduced the rate of relapse but at the cost of increased death from toxicity (partly because of insufficiently trained personnel). The rate of

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death from toxicity was less in the recent period than in the middle period, a finding we attribute to the training of nurses, 24-hour on-site physician coverage, ready access to intensive care, written evidence-based supportive care guidelines, and improved identification and treatment of comorbid conditions (eg, malnutrition, infection) at diagnosis.6,18-23 The private foundation, NACC, played an essential role in reducing the incidence of treatment abandonment from 16% in the early period to only 0.5% in the recent period by providing parents with transportation, housing, and work opportunities.

Work remains to be done. Death from toxicity is now the main preventable cause of treatment failure in childhood ALL in Recife and will be the focus of future efforts. We have implemented a modified remission induction regimen for patients with poor oral hygiene, infection, malnutrition, or other comorbid conditions at diagnosis. Further, chemotherapy is given at a reduced dose or is suspended until clinical recovery if patients experience toxic effects during remission induction therapy. Finally, community education and the training of community health agents and local pediatricians may facilitate earlier diagnosis.

As countries control the rate of death from infection, respiratory illness, and malnutrition, cancer becomes a leading cause of childhood mortality. In children aged 1 to 14 years, cancer is the leading cause of disease-related childhood death in the United States but the third leading cause in Brazil and fourth in El Salvador.20,24 Leaders in international pediatric oncology have summarized key elements of successful treatment of cancer in resource-poor countries: identification of local needs, mobilization of the community, partnership with an established center, development of a multidisciplinary health care team, improvement of supportive care, subsidized travel and housing for patients, and development of treatment protocols adapted to local conditions.17,25-27 Our findings confirm the importance of each of these elements,

The 5-year event-free survival estimate was 32% (95% confidence interval [CI], 21%-43%) in the early period (1980 to 1989), 47% (95% CI, 36%-58%) in the middle period (July 1994 to March 1997), and 63% (95% CI, 55%-71%) in the recent period (April 1997 to December 2002).

Table 3. Cause-Specific Treatment Failure in Childhood Acute Lymphoblastic Leukemia in Recife, Brazil, by Treatment Period*

<table>
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<tr>
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<tr>
<td>Relapsed or progressive disease</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No. of patients</td>
<td>12</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Probability (95% CI)</td>
<td>14 (10-20)</td>
<td>3.8 (1.9-7.8)</td>
<td>3.3 (2.0-5.3)</td>
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<tr>
<td>Relative risk (95% CI)</td>
<td>5.3 (2.1-13)</td>
<td>1.3 (0.3-5.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Death from infection</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No. of patients</td>
<td>5</td>
<td>9</td>
<td>21</td>
</tr>
<tr>
<td>Probability (95% CI)</td>
<td>6.0 (3.4-10)</td>
<td>12 (7.6-17)</td>
<td>9.8 (7.5-13)</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>0.6 (0.2-1.7)</td>
<td>1.3 (0.6-2.8)</td>
<td>1.0</td>
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<tr>
<td>Death from noninfectious toxicity†</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>2</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Probability (95% CI)</td>
<td>2.4 (1.0-5.8)</td>
<td>13 (8.7-19)</td>
<td>4.2 (2.7-6.4)</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>0.6 (0.1-2.7)</td>
<td>3.3 (1.3-8.1)</td>
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<td>Abandonment of therapy‡</td>
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<tr>
<td>No. of patients</td>
<td>13</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Probability (95% CI)</td>
<td>16 (11-22)</td>
<td>1.3 (0.4-4.3)</td>
<td>0.5 (0.1-1.6)</td>
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<tr>
<td>Relative risk (95% CI)</td>
<td>36 (4.7-277)</td>
<td>3.2 (0.2-51)</td>
<td>1.0</td>
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<tr>
<td>All causes</td>
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<tr>
<td>No. of patients</td>
<td>32</td>
<td>23</td>
<td>38</td>
</tr>
<tr>
<td>Probability (95% CI)</td>
<td>39 (32-46)</td>
<td>29 (23-36)</td>
<td>18 (15-21)</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>2.4 (1.5-3.8)</td>
<td>1.8 (1.1-3.1)</td>
<td>1.0</td>
</tr>
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</table>

Abbreviation: CI, confidence interval.
*Probability and relative risk are calculated for cause-specific treatment failure within 1 year of diagnosis.
†Predominantly tumor lysis syndrome and hemorrhage.
‡Defined as missing 6 or more consecutive weeks of treatment and follow-up.
which have led to success in El Salvador and other countries with limited resources.8,17,18,31 Essential for success is a dedicated, local, well-trained, full-time pediatric hematologist/oncologist who can identify correctable defects in the health care system and implement cost-effective changes; also crucial is the support of a private foundation that can lobby for change of the health care system, support patients and families economically, and raise money to assist with other needed improvements. Finally, clinical research is essential to identify the causes of treatment failure and adapt treatment protocols to local conditions, as demonstrated in Honduras, Chile, and Mexico.8,20,30 Studies of the impact of changes are essential in setting the priorities for future work and in demonstrating to governments and other potential sources of support that childhood cancer is indeed curable and can be cured largely with existing resources.31

Clearly, there remains a significant gap between the 80% cure rate for ALL in resource-rich countries and the 35% rate in many resource-poor countries. The high cure rates in Europe and the United States were achieved during 40 years, but our results demonstrate that proven treatment regimens can be adapted for use in a resource-poor setting in much less time. In Recife, the 5-year event-free survival increased from 32% to 63% in a decade. This progress reflects the use of a systematic approach to improve the pediatric oncology service and the important efforts of NACC to provide families with the necessary resources to ensure that their children will complete the complex, lengthy ALL chemotherapy regimen. Ninety-five percent of the budget comes from local resources, so a dedicated local team can make progress with even a small amount of external funding and ongoing technical assistance.

In conclusion, treatment of childhood ALL in a dedicated pediatric oncology unit using a comprehensive multidisciplinary team approach, protocol-based therapy, and a locally funded family support system is associated with improved outcome, even in areas with limited economic resources.

Author Contributions: Dr Howard had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.


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REFERENCES


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