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Results of Treating Childhood Acute Lymphoblastic Leukemia in a Low-middle Income Country: 10 Year Experience in Northeast Mexico

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Background and Aims. In high-income countries, treatment protocols for acute lymphoblastic leukemia (ALL) in children lead to a 5-year overall survival (OS) approaching 90%. There is scarce information on protocols and results of therapy from low-middle income countries (LMIC). We documented the results of treating children with ALL with two protocols in consecutive 5-year periods at a reference center in northeast Mexico.

Patients and Methods. Children ≤16 years of age diagnosed with ALL treated with two protocols were studied. Each protocol was used for 5 years; 246 children, 112 in protocol 1 and 134 in protocol 2, were included. Protocols were BFM-inspired and adapted from several regimens; protocol 2 was intended to decrease toxicity and need for hospitalization. Event-free survival (EFS) and overall survival (OS) were determined using the Kaplan-Meier method.

Results. In protocol 1, 103 patients (91.96%) achieved complete remission compared to 106 (79.10%) in protocol 2 ($p = 0.001$). The 5-year OS was 67.1% for protocol 1 vs. 55.5% for protocol 2, whereas EFS was 58.2% vs. 36.9%, respectively. Relapse occurred in 45 patients (40.17%) in protocol 1 vs. 42 (31.34%) in protocol 2 ($p = 0.181$). OS 1 year after relapse was 52.4% vs. 57.1%, respectively. No difference in relapse rate was documented.

Conclusions. No improvement in survival rates of children with ALL from a low-income group living in a LMIC was achieved over a decade. Implementation of contemporary protocols with a high success rate is mandatory. © 2017 IMSS. Published by Elsevier Inc.

Key Words: Acute lymphoblastic leukemia, Childhood leukemia, Chemotherapy, Low-middle income countries, Survival rates.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer. Modern combination chemotherapy, effective central nervous system (CNS) prophylaxis, and risk-adapted treatment protocols have dramatically improved survival and outcome to >80% across industrialized nations (1–4) and >90% in the U.S. (2). A more intense myelosuppressive therapy has led to lower relapse rates; however, in low-middle income countries (LMIC), there is concern that the increase in treatment-related morbidity and mortality could abrogate any reduction in relapse risk (5) and increase the costs of ALL therapy in an already restricted financial environment. Treatment regimens are usually developed over several years in multicenter efforts in one or several developed countries (6–9). Afterwards, they are regularly adopted with diverse modifications by centers in non-industrialized nations (10,11) with variable success rates. There are important issues to consider when choosing a treatment regimen for childhood ALL in

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countries with limited health budgets including, but not limited to, patient nutrition status (12,13), available hospital infrastructure and family support, health care system organization and resources, the ability to provide intensive supportive care (14) and the availability of specialized laboratory tests used in the diagnosis of leukemia and in patient management. In addition, the family's income and financial limitations should also be considered. Due to these factors and differences in the biological behavior of leukemic clones (15,16), the cure rates reported in LMIC range from 51−76% (10,11), lagging considerably behind high-income nations. The outcome differences between developed and developing countries could thus be a consequence of suboptimal therapy, lack of access to cancer care facilities, delay in the initiation of treatment, treatment-related toxicity, inherent ALL biological differences and abandonment of treatment (17), among other reasons. In consequence, the choice of an appropriate chemotherapy regimen with a high rate of adherence in LMIC should be carefully investigated; rigorous follow-up is also needed to address any obstacles in its implementation. In this context, switching from a well-established ALL chemotherapy protocol to a new protocol is a difficult decision because the expected benefits in terms of costs, toxicity, complications and survival rates as well as the logistics and capacity to respond to the challenges posed for such a decision must be carefully considered.

We report our 10-year experience treating children with ALL with two protocols at our regional reference center and adapted from different schemes with the goals of improving response rates and limiting hospitalization needs due to toxicity-related chemotherapy.

Patients and Methods

We included 246 patients ≤16 years of age with a diagnosis of ALL in a comparative, longitudinal, and retrospective study of two treatment regimens from 2004−2015 at the Hematology Service of the "Dr. José Eleuterio González" University Hospital of the School of Medicine of the Universidad Autónoma de Nuevo León in Monterrey, México. Information was retrieved from two sources, the hospital clinical files and the hematology electronic database. The study protocol was approved by the Institutional Review Ethics and Research Board at the hospital. Our hospital is a reference center for low-income uninsured patients from five states in northeast Mexico and receives mostly high-risk ALL children. The public medical insurance program ("Seguro Popular") has underwritten the cost of treatment for our patients diagnosed with ALL since the year 2004.

Diagnosis

ALL diagnosis was established by a detailed clinical history, physical examination and a complete blood count as well as peripheral blood (PB) smear and bone marrow (BM) aspirate morphological analysis. Immunophenotype determination and detection of minimal residual disease (MRD) was carried out by multiparametric flow cytometry using BD FACScalibur™ equipment (Becton-Dickinson, San Jose, CA). Steroid response was evaluated on day 8 of the induction phase. Response was considered good if <1000 blasts/mm^3 were present in PB; poor response was defined as ≥ 1000 blasts/mm^3 in PB. Complete morphological remission was defined by the presence of $<5\%$ lymphoblasts in BM at day 36. MRD was considered present if the disease burden was $>0.01\%$ at day 29 (18). CNS involvement was diagnosed if >5 leucocytes/mm^3 were counted in cerebrospinal fluid (CSF) and lymphoblasts were identified unequivocally in cytospin preparations (19) and CSF flow cytometry.

Patients were classified in high-risk and standard-risk groups according to established guidelines (20). Patients <1 year or ≥ 10 years of age, with $\geq 50{,}000 \times \mu$L WBC, infiltration of the CNS and/or testis at presentation, T-cell ALL, CALLA-, poor response to prednisone, or lack of remission after 33 days of starting induction therapy, were considered to be at high risk and were treated accordingly. Beginning in 2009, flow cytometry MRD studies were performed on day 29. Cytogenetic studies were not performed due to budget limitations. Relapse was diagnosed following accepted criteria for bone marrow, combined (21) and extramedullary relapses (22). Relapse occurring <18 months after diagnosis was defined as a very early relapse, a relapse occurring between 18 and 36 months was designed as an early relapse and that developing >36 months from diagnosis was classified as late relapse (21). The study was conducted in real-world circumstances in a low-income group of a LMIC country.

Treatment

Children were stratified into standard- and high-risk groups according to NCI Rome risk criteria to receive risk-adapted chemotherapy (23). Patients received two protocols designed at our center based on drug availability, the first one between January 2004 and April 2009 (Table 1). Induction included standard doses of prednisone (PDN), vincristine (VCR), L-asparaginase (ASP), and one or two doses of doxorubicin (DOX) in standard and high-risk children, respectively, plus four doses of intrathecal chemotherapy (IC) for CNS prophylaxis. Consolidation included single doses of cytosine arabinoside (Ara-C), 1.5 g/m^2 and methotrexate (MTX), 1.5 g/m^2 administered in a 24-h infusion. Afterwards, a month of daily 6-mercaptopurine (6MP) and weekly MTX was administered. Reinduction consisted of 14 day of prednisone, three doses of vincristine, two of doxorubicin for high and one for standard-risk patients, two doses of L-asparaginase and two of intrathecal CNS prophylaxis. Ten days after reinduction, maintenance was