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Secular trends and predictors of mortality in acute lymphoblastic leukemia for children of low socioeconomic level in Northeast Brazil

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ABSTRACT

Background: The treatment for ALL has evolved in recent decades and as a result survival rates are now close to 90% in many developed countries. However, this is not the case in developing countries where survival rates are often below 35%. More than 80% of children who are affected by ALL worldwide live in developing countries. The objective of this study was to evaluate the secular trend in mortality for children with ALL living in Sergipe, a state in northeastern Brazil, and to investigate any association with variables that relate to socioeconomic status.

Method: This study evaluated ALL patients who were less than 20 years of age and who were treated at the Dr. Osvaldo Leite Oncology Center in the capital city, Aracaju. The sample comprised two cohorts of patients from the public health service: patients treated from 1980 to 2004 (cohort A) and from 2005 to 2014 (cohort B). The findings were compared to those of patients treated in the one private service for pediatric cancer treatment available in the region, from 2005 to 2014 (cohort C). Two categories of variables were considered in this study: biological and socioeconomic.

Results: We analyzed 412 patients who were divided into three cohorts (cohort A: 287 patients, cohort B: 106 patients and cohort C: 19 patients). The mortality rates for the three cohorts were significantly different: 57.5% in cohort A, 45.3% in cohort B and 26.3% in cohort C ($p = 0.006$). Mortality during induction in cohort B was 22.6%, while in cohort C no deaths occurred during this phase ($p = 0.041$). Patients living in rural areas had higher mortality rates ($p = 0.036$).

Conclusions: The reduction in deaths from infection during induction seems to be the starting point for improving the chances for children and adolescents with ALL anywhere in the world.

1. Introduction

Acute lymphocytic leukemia (ALL) is the most common childhood cancer. The treatment for ALL has evolved in recent decades and as a result, survival rates are now close to 90% in many developed countries [1,2]. Multicenter therapeutic protocols based on sequential combinations of cytotoxic drugs, treatment of subclinical disease in the central nervous system and the extension of the maintenance phase of chemotherapy (two to three years) have made ALL a curable disease. Stratification by risks, the identification of prognostic factors and improvement in clinical support have also contributed to increased survival. However, this is not the case in developing countries where survival rates are often below 35% [3]. More than 80% of children who are affected by ALL worldwide live in developing countries [3–6].

The main causes of failure include abandonment, high relapse rates and higher treatment-related mortality [6]. Moreover, pediatric oncology services in developing countries face particular problems, often unknown in developed countries, such as the temporary or permanent lack of essential chemotherapic drugs, or limited access to surgery and radiotherapy [3,7].

Even when proper treatment is available, socioeconomic disparities, such as access to adequate health services, especially in rural areas, result in reduced survival rates [3,7]. It is challenging for patients to travel in order to receive specialized care and this is one of the factors that contribute to the abandonment of

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treatment in low socioeconomic areas. Ways to minimize this problem include temporary accommodation for the family, which results in improved adherence to therapy [7].

Elevated relapse rates and increased mortality resulting from treatment also compromise the survival of patients with ALL. In countries such as El Salvador, infection is the most common complication associated with chemotherapy. In addition, a low level of parental education is associated with a poor prognosis in cases of sepsis [8]. Relapses are often related to the inability or failure to perform the complex treatment protocols [9].

The objective of this study was to evaluate the secular trend and the predictors of mortality for children with ALL living in Sergipe, a state in northeastern Brazil, and to assess the potential association with variables related to socioeconomic status.

2. Materials and methods

This research project was approved by the Ethics Committee on Research involving Human Subjects at the University Hospital of the Federal University of Sergipe. All patients older than 18 years old signed an informed consent form; for patients under 18 years old, a form was signed on their behalf by a parent or guardian.

2.1. Setting

Brazil is the largest country in South America and the world's fifth largest by land area. It has a population of 190 million inhabitants according to the 2010 census [10]. Income inequality is still significant in Brazil, despite the reduction in extreme poverty over the last three decades. Although the average household income per capita in Brazil was USD 294 in 2010, 25% of the population received USD 82 and there was a higher incidence of poverty in medium-sized cities (10–50,000 inhabitants) [10].

The illiteracy rate in Brazil is estimated to be 8.7% for people aged 15 years or more, a group comprised of 13.2 million people in 2012. More than half of this group (54%; 7.1 million people) live in the Northeast of Brazil [10].

Sergipe is one of the 27 federal units of Brazil. It is located in the Northeast and it is limited by the Atlantic Ocean to the east, by the state of Bahia to the west and south and by the state of Alagoas to the north. It occupies an area of 21,915 km^2 and has a population of 2,068,017 inhabitants. Sergipe's main city, Aracaju, places 14th in relation to other Brazilian state capital cities with regard to annual per capita income (BRL 1239.56). Aracaju has a population of 570,937 inhabitants and 36.74% of them are younger than 20 years old [10]. Due to Sergipe's small geographical area, the most distant city (Caninde do São Francisco) is located 213 km from Aracaju [11].

This study was conducted at the pediatric service of the Dr. Osvaldo Leite Oncology Center, which is part of the National Health System and is the single public service for pediatric cancer treatment in the state of Sergipe. The Dr. Osvaldo Leite Oncology Center is located in the capital city, Aracaju, and it is linked to the only public general hospital of Sergipe.

2.2. Population

This study focused on ALL patients who were less than 20 years of age. The Pediatric service of the Dr. Osvaldo Leite Oncology Center receives virtually all patients with cancer in the state of Sergipe attended by the public health system as well as some patients (about 20%) living in cities close to the border of Sergipe, in the states of Bahia or Alagoas.

The ALL diagnosis was confirmed by immunophenotyping bone marrow aspirate or peripheral blood, and the patient was treated by a team of pediatric oncologists. Two "Supporting Houses" (non-governmental organizations providing social and economic assistance to pediatric oncology patients and their families) were available. They offered accommodation, food and transport to all patients in treatment or in follow up, and some drugs and complementary tests.

The chemotherapy protocol used was proposed by the Brazilian Group Treatment in Childhood Leukemia (GBTLI-99) and is the standard protocol in Brazil. It consists of four phases: induction of remission, intensification, re-intensification and maintenance. The induction phase includes the first 42 days of treatment. After a patient's hematological recovery and confirmation of remission by bone marrow examination, the intensification phase follows, lasting 12 weeks and is followed by the re-intensification (12 weeks) and finally the maintenance phase (84 weeks) [12].

Patients are stratified at diagnosis into two groups: low risk and high risk of relapse. High-risk patients were defined as follows: those aged 0–12 months old, those older than nine years old and those who have a white blood cell count equal to or greater than 50,000 cells/mm^3 at the diagnosis or immunophenotype compatible with T cell ALL. The low-risk group comprised patients who did not fall in to any of these categories [12].

First relapse patients were treated with the BFM-95 protocol [13] and those in the second relapse were treated with St Jude Total XV [14]. All patients received sulfamethoxazole and trimethoprim for *Pneumocystis jiroveci* prophylaxis.

2.3. Procedure

The sample was composed of two cohorts of patients from the public health service: patients treated from 1980 to 2004 (cohort 1980–2004) and from 2005 to 2014 (cohort 2005–2014 Public). The findings were compared to those of patients treated in the one private service for pediatric cancer treatment available in the region, by the same team and protocols, from 2005 to 2014 (cohort 2005–2014 Private). Data from cohort 1980–2004 were obtained retrospectively from a pre-existing database, while data from cohorts 2005–2014 Public and 2005–2014 Private were obtained prospectively. Demographic and socioeconomic data from cohorts 2005–2014 Public and 2005–2014 Private were obtained through routine socioeconomic interview with the primary caregiver at the beginning of treatment. The database used to source cohort 1980–2004 did not include demographic and socioeconomic data.

The cohort 1980–2004 was analyzed as a historical reference, since that chemotherapy protocols used at that time differ substantially from those adopted presently as well as the quality of the supportive care. The cohorts 2005–2014 Public and Private were compared, although the sample sizes had been quite different. Although the sample size may not be sufficient to ensure confidence in the statistical comparisons, it reflects the actual distribution of cancer patients studied region, since the minority of the families have financial resources to use health insurance in cancer treatment.

Data for losses in the cohort 1980–2004 were not available, but considering that it was the only public pediatric oncology service of the state of Sergipe; it can be assumed that, if there were losses for transfer or refusal, they should have been numerically insignificant. In cohorts 2005–2014 Public and 2005–2014 Private there were no losses by abandonment, refusal of treatment or transfer to other services, after the formalization of partnership with the first "Supporting House", in May 2004.

2.4. Outcome measures

Treatment failure was considered in the cases that resulted in: abandonment of treatment, treatment-related death (unrelated to relapse) and relapse of the disease. Abandonment was defined as the refusal of the patient or his/her caregiver to continue the treatment, or the failure to attend chemotherapy sessions for more than eight weeks. Deaths related to chemotherapy toxicity were divided into three groups: infection, bleeding and tumor lysis syndrome. Relapse was defined as disease recurrence after complete remission of ALL. Death during induction was defined as the death that occurred during the first 42 days of treatment. These definitions have been previously used by other authors [3,6,15]. The overall five-year survival was evaluated for the three cohorts.

2.5. Potential predictors

Two categories of variables were considered in this study: biological and socioeconomic [6]. The biological variables studied were: age, sex, category defined by immunophenotyping (B or T lymphoblasts), and risk of relapse (low or high risk). The socioeconomic variables were: family income, education level of the main caregiver, number of persons residing in the patient's home, housing conditions (presence or absence of clean water and sanitation), place of residence (rural or urban area) and type of medical assistance received (public or private). The main caregiver was defined as the person responsible for the child, with no remuneration for this activity. Families who received less than half the Minimum Wage per capita each month, or total monthly income of up to three Minimum Wages have been classified as low income as defined by Decree No. 6135 of 26/06/2007 from the Presidency of the Republic of Brazil, which is still valid today [16]. The current value of the Minimum Wage is equivalent to USD 277 and is defined as the lowest amount that an employee can receive in order to pay their expenses. The educational level of the main caregiver was classified according to the total number of years studied: less than eight years of study (including illiterates and incomplete primary education), and eight or more years of study (completed primary education or higher).

2.6. Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 17.0. Categorical variables were described as absolute and relative frequency and continuous variables as mean and standard deviation. Chi-Square Test or Fisher's Exact Test evaluated associations between categorical variables and the Kruskal–Wallis Test evaluated association between continuous variables that did not meet the normality criterion. Overall survival in each cohort was estimated using the Kaplan–Meier method and compared using the Log-Rank Test, and $p < 0.05$ was considered statistically significant.

3. Results

We analyzed 412 patients who were divided into three cohorts (cohort 1980–2004: 287 patients, cohort 2005–2014 Public: 106 patients and cohort 2005–2014 Private: 19 patients). Only one