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OVERALL SURVIVAL IN PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA TREATED WITH CALGB 8811 PROTOCOL IN LOW INCOME COUNTRY

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ABSTRACT

Introduction: ALL is known to have a lower survival rate in adults and this can be attributed, among other aspects, to intolerance to intensive regimens. As the treatment of ALL is very complex, with many protocols available, this study proposes an analysis regarding the CALGB 8811 protocol in a tertiary health unit in Ceará.

Methods: In this retrospective study, 50 patients with a recent diagnosis of ALL who underwent the CALGB8811 protocol were evaluated. Disease risk criteria were based on the CALGB8811 protocol.

Results: CR was obtained in 86% of patients. 12% of patients died during induction due to infectious complications. 30% of patients underwent alloSCT, 60% were on CR1.

The median overall survival (OS) was 21.5 months (8.1-38.7). The 5 years OS was 25% in the transplanted patients versus 60% in the transplanted group. Achieving complete remission after induction chemotherapy and allogeneic hematopoietic stem cell transplantation were the factors associated with better long-term survival rates in uni and multivariate analysis.

Conclusion: Risk factors classically associated with worse adult ALL outcome and post-induction MRD status were not outcome predictors, in addition, post-induction remission and alloSCT were factors associated with a favorable outcome.

Keywords: acute lymphoblastic leukemia. CALGB 8811 protocol. hematopoietic stem-cell transplantation.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a hematological malignancy with high survival rates among children through protocols with multiagents intensive chemotherapy [1]. Adults patients have an inferior overall survival (OS) mainly due intolerance to intensive regimens and because an adverse disease biology [2].

Treatment of adult ALL is complex with many available protocols [3-4] based on corticosteroids, anthracyclines, alkylating agents, methotrexate and L-asparaginase. Complete remission (CR) rates after induction are high, but many patients relapse during or after chemotherapy leading to a low long term OS. In this context, disease risk stratification is important because it defines patients who should be referred to allogeneic hematopoietic stem-cell transplantation (HSCT) in first remission [5].

The CALGB 8811 protocol has a multidrug design, consisting of an induction, intensification, central nervous system (CNS) prophylaxis and maintenance phases. It was initially evaluated in a phase II mul-

ticenter trial with high rates of CR, especially in patients under 30 years with prolonged leukemia free survival [2].

Treating adults ALL is challenging in the context of the Brazilian public health system because it requires a tertiary healthcare facility with an onco-hematological ward, a day hospital structure to provide sequential outpatient chemotherapy, and a HSCT unit.

Previous studies in Brazil demonstrated particular points that interfere in clinical outcomes in ALL patients, such, difficulties in the treatment of infections, absence of, clinical trials and, the lack of High Efficiency Particulate Arresters (HEPA) filters in induction and allogeneic HSCT phases [6].

There are few studies evaluating different protocols in low income countries[7]. In this retrospective study we report the outcomes of adult ALL patients treated with CALGCB 8111 protocol in a public tertiary single center located in northeast Brazil.

METHODS

Study Design and Patients:

This was a retrospective study conducted from March 2011 to December 2018 at Hospital Universitário Walter Cantídio of Federal University of Ceará. Patients with newly diagnosis ALL who underwent CALGB8811 protocol during the proposed period were evaluated. Patients younger than 18 years, with a diagnosis of biphenotypic or mixed lineage leukemia and with a previous diagnosis of chronic myeloid leukemia were excluded from the analysis.

Disease risk criteria were based on the CALGB8811 protocol. High risk patients were those with WBC more than 30 000/mm^3 in B-ALL; more than 100 000/mm^3 in T-ALL; more than 35 years aged; BCR-ABL1 positivo B-ALL; complex karyotype (more than 3 chromosomal alterations).

The indications to allogeneic HSCT were High risk ALL; relapsed ou refractory ALL. We defined relapsed ALL in patients that had a recurrence after 6 months of response. We defined refractory ALL in patients that do not achieve CR in first induction or patients who relapsed before 6 months.

Disease assessment

We defined ALL based on 2008 WHO classification. The phenotypic definition was based in flow cytometry analysis. Karyotype was made by classical cytogenetic analysis in Giemsa and BCR-ABL1 analysis was made by PCR.

CR was defined by less than 5% of blasts in bone marrow aspirate at the end of induction. Treatment related mortality (TRM) was defined as death for any cause, except in the setting of relapsed disease.

Minimal residual disease (MRD) was made at the end of induction and before the alloSCT. Patients with BCR-ABL1 negative ALL, analysis of MRD was made by flow cytometry. Patients with BCR-ABL1 positive ALL, MRD was investigated by flow cytometry and PCR.

Statistics

Data analysis was performed using the R program., Results with p-value < 0,05 were considered statistically significant. Survival curves were performed by the Kaplan-Meier method, and the groups were compared using the log-rank test. The univariate and multivariate analysis was made with R program. Data from patients undergoing allogeneic HCT were also recorded, and patients were not censored at the time of transplantation.

Results

During the study period 50 patients with de novo ALL were admitted. The male / female ratio was 1.4 (29/21) and the mean age was 34.4 (18-74, SD=16.1 years). Most patients (62.0%) analyzed at diagnosis had high-risk criteria. The demographic characteristics are in Table 1.

CR was obtained in 86 % patients . 12% of patients died during induction by infection complications. 30% patients underwent alloSCT, 60% were in CR1.

The median overall survival (OS) was 21.5 months (8.1-38.7) (Figure1). The 5 years OS was 25% in no transplanted patients versus 60% in the transplanted group (Figure 2). OS was not statistically different according to age, immunophenotype (B versus T ALL) or risk groups.

There was a statistically difference on Cox regression model between patients who underwent allogeneic HSCT, independently of time of remission (HR=1.34; p-value = 0.01) and patients who achieved CR1 (HR=4.6; p-value<0.001) (Table 2).

The overall survival of patients with ALL who underwent the CALGB8811 protocol had no influence by gender, age over 35 years, risk stratification, immunophenotype and MRD scores in uni and multivariate (logistic regression) analysis. Although achieving complete remission after induction chemotherapy and allogeneic hematopoietic stem cell transplantation were the factors associated with better long-term survival rates in uni and multivariate analysis.

Discussion

ALL is a more common haematological malignancy in children than in adults [8]. In pediatric patients, cure rates with intensive chemotherapy regimens may reach up to 90-95% [7]. In adults, cure rates are lower, with a high relapse rate after induction, especially in patients at unfavorable risk.

Classically, the main risk factors are leukocytes above 30000 / mm^3 in B-ALL and 100000 / mm^3 in T-ALL; age over 35 years; unfavorable cytogenetics (BCR-ABL1 positive ALL;t(4;11); Ph-like kinase profile; hypodiploid and complex karyotype) [9-10].

Modernly other risk factors are being added to the analysis, especially post-induction MRD which has been shown to be a good predictor of long-term response and surrogate of favorable outcome after alloSCT [10].

These risk factors have not been studied in the Brazilian population although many centers use these variables to define indication for allogeneic hematopoietic stem cell transplantation (alloSCT) in first remission [11].

Some studies have shown that patients with standard risk ALL and post-induction negative DRM would not benefit from first remission alloSCT. In the present study, however, the risk factors classically used in the CALGB8811 protocol and negative post-induction DRM were not good predictors of favorable outcome in univariate analysis, nor were they associated with longer survival.

The two main factors that were associated with better outcome and higher median overall survival were post-induction morphological remission (data not shown) and alloSCT. The present study did not evaluate the reasons why the risk factors established in international studies were not predictors of better outcomes in the northeast Brazil reality; however, possible reasons for non-reproducibility are the relatively small patient sample, difficulties in stratifying patients better by flow cytometry and MRD analysis, hospital infrastructure in the single health system, low human development index of patients treated and delayed arrival of acute leukemia patients in specialized services[11].

Conclusions

Risk factors classically associated with worse adult ALL outcome and post-induction DRM status were not predictors of outcome in the northeast Brazilian reality. Post-induction remission and alloSCT were factors associated with a favorable outcome. In this context, the need for further studies evaluating such risk factors in Brazilian context is reinforced.

FIGURE1 - Overall survival of patients with ALL treated with GALGB8511

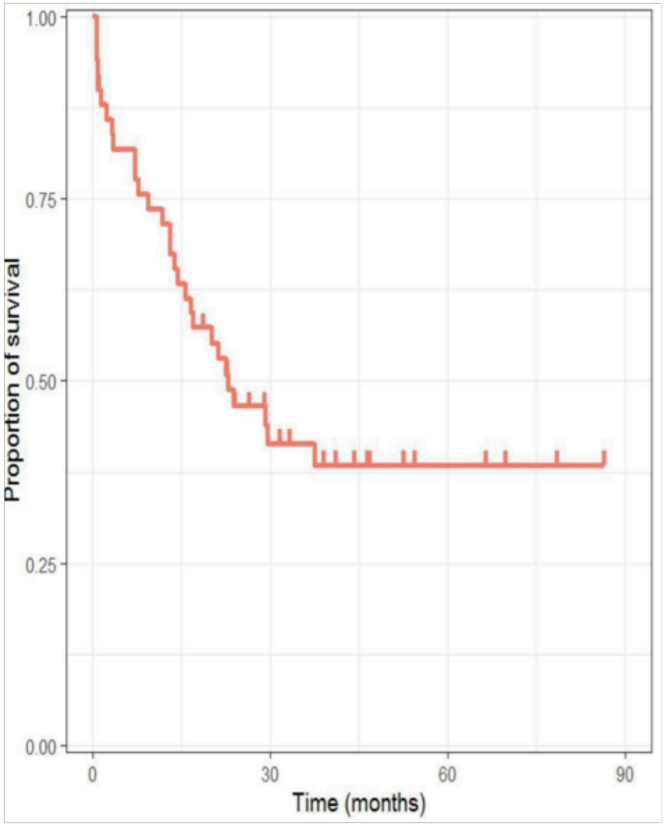

FIGURE2 - Overall survival according hematopoietic stem cell transplantation

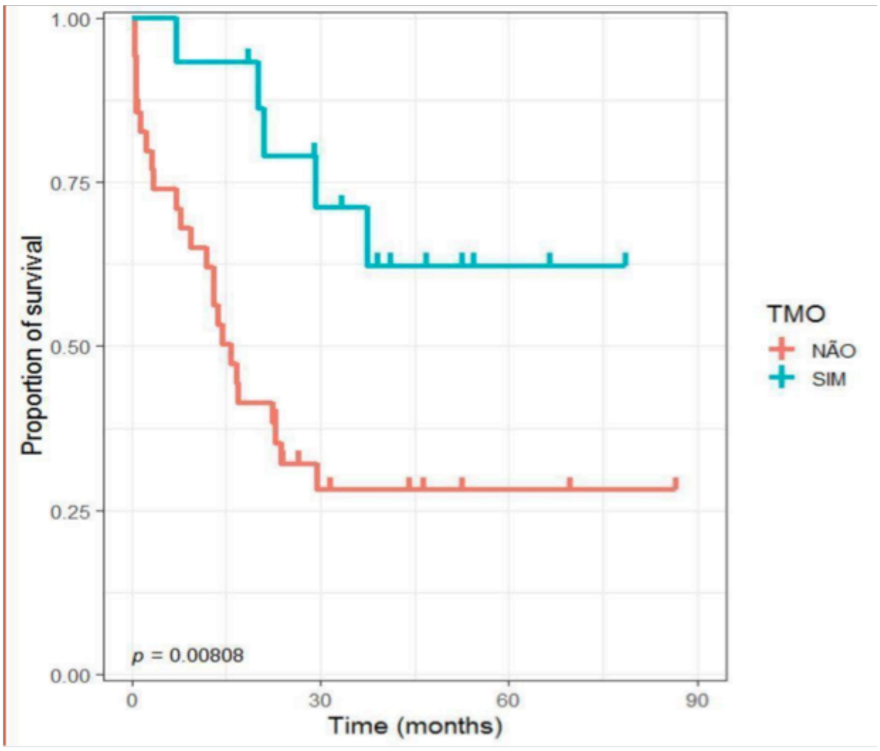

TABLE 1 - patients demographics

Variables	N(%)
Sex	
Female	21 (42)
Male	29 (58)
Age	
Below 35 years	30 (60)
Above 35 years	20 (40)
Immunophenotype	
B-ALL	40 (80)
T-ALL	10 (20)
GALB 8811 risk stratification	
Standard	31 (62)
High	19 (38)
CR1	
Achieved	43 (86)
Not achieved	7 (14)
alloSCT	
Yes	15 (30)
No	35 (70)

TABLE 2: Cox regression model analysis. Age was analyzed as continuous indepedent variable; sex was analyzed in dichotomous independent variable (1 as male); CALGB risk stratification was analyszed as dichotomous independent variabel (1 as high risk), also CR1 and alloSCT.

Variables	HR	p-value
Age	0.01	0.3
Sex	0.78	0.1
GALGB 8811 risk stratification	0.6	0.2
CR1	4.6	<0.001
alloSCT	1.34	0.01

REFERENCES

[1] Jain N, Lamb AV, O'Brien S, Ravandi F, Konopleva M, Jabbour E, et al. Early T-cell precursor acute lymphoblastic leukemia/lymphoma (ETP-ALL/LBL) in adolescents and adults: a high-risk subtype. Blood. 2016;127(15):1863-9.

[2] Larson, RA, Dodge RK, Burns CP, Lee EJ, Stone RM, Schulman P, et al.

A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: cancer and leukemia group B study 8811. Blood. 1995;85(8):2025-37.

[3] Larson, RA, Dodge RK, Linker CA, Stone RM, Powell BL, Lee EJ, et al. A randomized controlled trial of filgrastim during remission induction and consolidation chemotherapy for adults with acute lymphoblastic leukemia: CALGB study 9111. Blood. 1998;92(5):1556-64.

[4] Awasthi A, Ayello J, Van de Ven C, Elmacken M, Sabulski A, Barth MJ, et al. Obinutuzumab (GA101) compared to rituximab significantly enhances cell death and antibody-dependent cytotoxicity and improves overall survival against CD20(+) rituximab-sensitive/-resistant Burkitt lymphoma (BL) and precursor B-acute lymphoblastic leukaemia (pre-B-ALL): potential targeted therapy in patients with poor risk CD20(+) BL and pre-B-ALL. Br J Haematol. 2015;171(5):763-75.

[5] Nachman J, Siebel N, Sather H, Steinherz P, DeLaat C, Fryer D, et al. Outcome for Adolescent and Young Adults 16–21 years of age (AYA) with Acute Lymphoblastic Leukemia (ALL) Treated on the Children' s Cancer Group (CCG) 1961 Study. Blood. 2004;104(11):683.

[6] Silva WF Junior, Medina AB, Yamakawa PE, Buccheri V, Velloso ED, Rocha V. Treating Adult Acute Lymphoblastic Leukemia in Brazil —Increased Early Mortality Using a German Multicenter Acute Lymphoblastic Leukemia-based regimen. Clin Lymphoma Myeloma Leuk. 2018;18(6):e255-9.

[7] Portugal RD, Loureiro MM, Garnica M, Pulcheri W, Nucci M. Feasibility and Outcome of the Hyper-CVAD Regimen in Patients With Adult Acute Lymphoblastic Leukemia. Clin Lymphoma Myeloma Leuk. 2015;15(1):52-7.

[8] Rytting ME, Jabbour EJ, Jorgensen JL, Ravandi F, Franklin AR, Kadia TM, et al. Final results of a single institution experience with a pediatric-based regimen, the augmented Berlin-Frankfurt-Munster, in adolescents and young adults with acute lymphoblastic leukemia, and comparison to the hyper-CVAD regimen. Am J Hematol. 2016;91(8):819–23.

[9] Deitcher OR, O'Brien S, Deitcher SR, Thomas DA, Kantarjian HM. Single-Agent Vincristine Sulfate Liposomes Injection (Marqibo) Compared to Historical SingleAgent Therapy for Adults with Advanced, Relapsed and/or Refractory Philadelphia Chromosome Negative Acute Lymphoblastic Leukemia. Blood. 2011;118(21):2592.

[10] Gokbuget N, Kneba M, Raff T, Trautmann H, Bartram CR, Arnold R, et al. Adult patients with acute lymphoblastic leukemia and molecular failure display a poor prognosis and are candidates for stem cell transplantation and targeted therapies. Blood. 2012;120(9):1868-76.

[11] Silva AL Junior, Alves FS, Kerr MW, Xabregas LA, Gama FM, Rodrigues MG, et al. Acute lymphoid and myeloid leukemia in a Brazilian Amazon population: Epidemiology and predictors of comorbidity and deaths. PLoS ONE. 2019;14(8):e0221518.