Chemotherapy induces plasmatic antioxidant changes in pediatric patients with acute lymphoid leukemia B that correlate to disease prognosis

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ABSTRACT

Pediatric acute lymphoid leukemias (ALL) is the most common childhood cancer, and cytotoxic chemotherapy remains the primary treatment option. Chemotherapic drugs act by oxidative stress generation, but their clinical meaning is poorly understood. During the chemotherapy schedule, this study evaluated the antioxidant profile of peripheral blood samples from 34 patients diagnosed with type B-cell ALL (B-ALL). Peripheral blood samples were collected at diagnosis (D0) and during the induction, consolidation, and maintenance phases. The plasma total antioxidant capacity (TRAP) was determined using the high-sensitivity chemiluminescence technique. Antioxidant levels were higher on D0 compared to day 7 after treatment starting (D7) in the induction phase (28.68–1194.71 μM Trolox, p = 0.0178) and in the high-risk group (age > ten years and/or with white blood cell counts and/or > 50,000 white blood cells/m3 at diagnosis) concerning low-risk patients (253.79–1194.71 μM Trolox, p = 0.0314). Reduced TRAP was also detected in patients who died compared to those who survived (392.42–1194.71 μM Trolox, p = 0.0278). Patients under consolidation (56.14–352.05 μM Trolox, p=<0.0001) and maintenance (30.48–672.99 μM Trolox, p=<0.0001) showed a significant reduction in TRAP levels compared to those from the induction phase (28.68–1390.26 μM Trolox), reaching levels similar to cured patients out of treatment (64.82–437.82 μM Trolox). These findings suggest that the variation of the total antioxidant capacity in B-ALL during chemotherapy is a parameter that correlates to some predictors of disease prognosis.

1 Introduction

Neoplasms are the leading cause of death in children worldwide (Steliarova-Foucher et al., 2017), corresponding to the second cause of death in children and adolescents in Brazil and developing countries are therefore considered a Public Health problem (INCA, 2017). In this group, pediatric leukemias stand out; cancers of the hematopoietic system are mainly characterized by the malignant transformation of lymphoid progenitor cells and, less commonly, of cells of the myeloid lineage (Saraiva et al., 2018; Malard and Mohty, 2020).

In recent decades, due to improved treatment, there has been a significant change in the prognosis and survival of these patients, the latter being primarily affected by disease recurrence (Rose-Inman and Kuehl, 2017; Brown et al., 2021; Short et al., 2021). According to the Children's Oncology Group (2021), disease survival increased from 83% to over 90% between the years 1990–2000. On the other hand, despite this significant improvement, relapse/recurrence rates of disease during childhood continued to be approximately 20%, with 5-year survival rates of only 30–50% after the first relapse and less than 20% for subsequent ones (Pehlivan et al., 2018; Chen et al., 2021).

Thus, survival in acute lymphocytic leukemia (ALL), in general, is greater than 80% (Rose-Inman and Kuehl, 2017; Brown et al., 2021).

Despite this, some patients do not respond to treatment and whose molecular mechanisms of therapeutic failure are little discussed. In this context, there is a great scarcity of information regarding the role of molecular mediators of the inflammatory response, cytokines, immune system proteins, and components of the oxidative stress response, both in the pathophysiology and the clinical outcome of the disease. In this sense, research for molecular biomarkers associated with ALL biology is a promising area that can help elucidate several unsolved issues (Hooke et al., 2020; Chen et al., 2021).

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The oxidation process is a regular biological event that involves the removal of electrons from a molecule which, in turn, will form a free radical. These are highly reactive molecules capable of breaking and forming chemical bonds in their environment, damaging DNA and RNA during the cell cycle (Hooke et al., 2020; Dong et al., 2021).

For this reason, cells manage antioxidants to prevent constant damage, reducing free radicals, and thus maintaining homeostasis.

When this balance between oxidants and antioxidants is altered, the result is a wide variety of systemic problems such as diabetes, cardiovascular disease, and cancer, including leukemias (Buettner et al., 2013; Dong et al., 2021). Redox balance acts on the normal hemopoiesis that occurs in the bone marrow, and the levels of antioxidants are primordial regulators of survival and quiescence of hematopoietic stem cells (Hole et al., 2011; Di Martino et al., 2021; Chen et al., 2021). Thus, depending
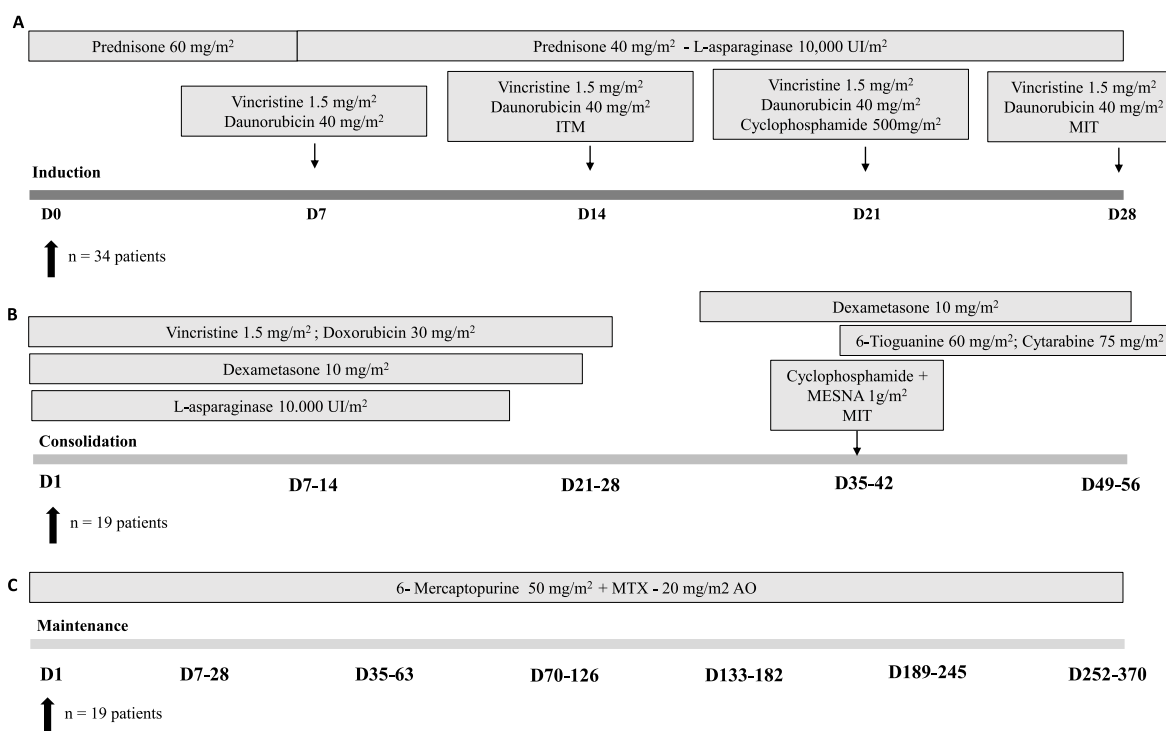

Fig. 1. Design of the study. Chemotherapeutic treatment scheme for type B Acute Lymphocytic Leukemia (B-ALL). A – Induction: Prednisone 60mg/m2 is administered orally (AO) from D1 to D7, after which the dose is reduced to 40 mg/m2 daily, orally, divided into two to three doses for three weeks (D8-D29), with regressive suspension in 3–4 days. If necessary, prednisone can be administered intravenously (IV), divided into three doses. Vincristine - 1.5g/m2/week, IV, with a maximum dose of 2 mg, given on days 8, 15, 22, and 29. Daunorubicin – 40mg/m2/week, IV, given on days 8, 15, and 22. L -asparaginase – 10,000 IU/m2 intramuscularly or IV (if thrombocytopenia <75,000/mm3) every three days, starting on day 8 of treatment, for nine doses. Cyclophosphamide – 500mg/m2 IV on days 22 and 23 of induction for patients classified in subgroups as slow responders. Intrathecal Medication (ITM) - triple therapy with methotrexate, Ara-C, and dexamethasone will be administered in age-adjusted doses on days 15 and 29 of induction (>1 < 3 years: 10mg/m2 and 20mg/m2 for methotrexate and Ara-C respectively; >3 < 9 years: 12mg/m2 and 24mg/m2, respectively; >9 years: 15mg/m2 and 30mg/m2, respectively. The maximum dose of dexamethasone is uniform (2mg/m2. Max. 2 mg B – Consolidation: Dexamethasone 10 mg/m2, orally, from D1 to D22, with gradual dose reduction, Vincristine 1.5 mg/m2, and Doxorubicin 30 mg/m2, IV, on D8, D15, D22, and D29. In addition, L-asparaginase 10,000 IU/m2, IM, on D8, D11, D15, and D18. Cyclophosphamide with Mesna 1000 mg/m2, IV, on D36. Thioguanine 60 mg/m2, AO, of D36 to D49 associated with Cytarabine 75 mg/m2, IV, D38 to D41, and D45 to D48. Intrathecal methotrexate with dose adjusted according to age from D38 to D45. C- Maintenance: The total duration of maintenance treatment is 24 months (104 weeks), calculated from the beginning of the induction. 6-mercaptan 50 mg/m2 orally once a day and methotrexate 20 mg/m2 orally once a week are given. Reference: Brazilian Group of Childhood Leukemia Treatment Schemes - GBTLI-LLA, 2009.

on the availability of antioxidants in the bone marrow, hematopoietic stem cells may stop multiplying and go into apoptosis, compromising average blood production.

Another critical issue is that the treatment itself has as its pro-apoptotic mechanism of action the generation of oxidative stress, a strategy that can compromise antioxidant levels in a systemic way (Hockenberry et al., 2014). Overall, antioxidant defenses are reduced in several types of leukemia (Tahir et al., 2017), and the activity of anti-oxidant enzymes such as superoxide dismutase and catalase are found to be reduced in newly diagnosed children (Battisti et al., 2008; Senturker et al., 1997). Despite this, information on the systemic status of anti-oxidants in leukemia studies is poor and the clinical meaning of anti-oxidants in newly diagnosed type B cell ALL (B-ALL) patients during different chemotherapy stages is not well-understood.

Therefore, this study focused on determining the systemic antioxidant status of B-ALL patients and investigating the impact of chemotherapy in various stages of treatment. Also, it evaluated the clinical meaning of this marker in the context of B-ALL.

2 Methods

2.1. Ethical aspects, study population, and treatment protocol

This study was conducted following the institutions' bioethics and research protocols and was approved by the Institutional Ethics Committee (24498213.0.0000.5231). All those responsible for the patients signed an informed consent form.

A total of 34 patients with B-ALL were selected according to the following criteria: age between 0 and 18 years; both sexes; with a confirmed diagnosis of B-ALL by myelogram and immunophenotyping, without infection at diagnosis, treated at the Cancer Institute of Londrina, Paraná, Brazil. A group of one hundred fifty (n = 150) healthy volunteers (10,5 years on average), out of chemotherapy treatment and without current infection, were included as a control group. All patients were treated with the same standard chemotherapy protocol, receiving the same drug combinations but subdivided according to the induction, consolidation, and maintenance phases of the GBTLI-LLA, 2009 protocol, as illustrated in Fig. 1.

2.2. Treatment protocol

The chemotherapeutic treatment scheme for type B Acute Lymphocytic Leukemia (B-ALL) was divided into three main phases: A, B, and C. The treatment days are referred to as D, followed by the respective number of treatment days.

Induction (phase A): Prednisone 60 mg/m^2 is administered orally (VO) from D1 to D7, after which the dose is reduced to 40 mg/m^2 daily, divided into two to three doses for three weeks (D8 – D29), with regressive suspension in 3–4 days. If necessary, prednisone can be administered intravenously (IV), divided into three doses. Vincristine 1.5 g/m^2/week, IV, with a maximum dose of 2 mg, given on days 8, 15, 22, and 29. Daunorubicin – 40 mg/m^2 per week, IV, given on days 8, 15, and 22. L-asparaginase – 10.000 IU/m^2 intramuscularly or IV (if thrombocytopenia <75.000/mm^3) every three days, starting on day 8 of treatment, for a total of 9 doses. Cyclophosphamide – 500 mg/m^2 IV on days 22 and 23 of induction for patients classified in subgroups as slow responders. Intrathecal Medication (ITM) triple therapy with metho-trexate, Ara C, and dexamethasone were administered in age-adjusted doses on days 15 and 29 of induction (>1 < 3 years: 10 mg/m^2 and 20 mg/m^2 for methotrexate and Ara C respectively; > 3 < 9 years: 12 mg/m^2 and 24 mg/m^2 respectively; > 9 years: 15 mg/m^2 and 30 mg/m^2, respectively. The maximum dose of dexamethasone is uniform (2 mg/m^2 Max. 2 mg).

Consolidation (phase B): Dexamethasone 10 mg/m^2, orally, from D1 to D22 with gradual dose reduction, Vincristine 1,5 mg/m^2 and Doxorubicin 30 mg/m^2, IV on D8, D15, D22 and D29. In addition, L-

asparaginase 10,000 IU, IM, on D8, D11, D15, and D18. Cyclophosphamide with Mesna 1000 mg/m^2, IV, on D36. Thioguanine 60 mg/m^2, VO, of D36 – D49, associated with cytarabine 75 mg/m^2, IV, D38 – D41, and D45 to D48. Intrathecal methotrexate with dose adjusted according to age from D38 to D45.

Maintenance (phase C): the total duration of maintenance treatment is 24 months (104 weeks), calculated from the beginning of the induction. 6 mercaptan 50 mg/m^2 orally once a day and methotrexate 20 mg/m^2 once a week are given. Reference: Brazilian Group of Childhood Leukemia Treatment Schemes – GBTLI-LLA, 2009.

2.3. Sample obtention

Peripheral blood anticoagulated samples (PB, 5 mL in EDTA) were collected by venipuncture from patients at diagnosis (D0) and during each chemotherapy treatment phase according to the protocol of the Brazilian Childhood Leukemia Treatment Group (induction, consolidation, and maintenance) (GBTLI-LLA, 2009). Samples were centrifuged at 4000 rpm for 5 min to obtain plasma and stored at −20 °C until analysis.

Clinical information (leucometry, platelet count, minimal residual disease, hemoglobin levels, classification for response to treatment) was collected from the medical records. Regarding the risk classification, the high-risk group consisted of patients whose white cell count at diagnosis (D0) was >50000/mm^3 and aged less than one year or more than ten years. The others were considered low risk.

2.4. Determination of Total Plasma Antioxidant Capacity (TRAP) by high sensitivity chemiluminescence (Repetto et al., 1996; Broto et al., 2021)

The procedure uses the compound (2,2′-azobis ABAP) that reacts with polyunsaturated fatty acids in the aliquot of blood plasma. This reaction emits photons in low quantity, not detectable by spectrophotometry. Thus, it is necessary to add luminol, an unstable compound capable of capturing the unpaired electrons of the antioxidants, amplifying the photon emission reaction, chemiluminescence, which was captured by the Glomax Promega luminometer, USA) at five readings per second with a total average time analysis period of 15 min. Thus, the greater the number of antioxidants present in the analyzed sample, the greater the light emission, represented by the delay in the rise of the ABAP curve compared to a control curve for tocopherol (hydrosoluble vitamin E, Trolox).

2.5. Statistical analysis

For the statistical analyses, the variables were analyzed according to the statistical assumptions of normality (Shapiro-Wilk test) and homoscedasticity (Levene's test). All analyzes were performed in duplicate, with data expressed as median (for non-parametric data) and minimum and maximum values or mean (for parametric data) ± standard error of the mean. The data were subjected to the Grubbs test to detect outliers, and no outliers were detected. Results were compared by Student's t-test, Mann-Whitney test or analysis of variance (ANOVA) followed by Bonferroni or Mann-Whitney test (comparisons between all groups), according to the distribution of variances and the number of compared groups, considering $p < 0.05$ as significant. All statistical analyzes were performed using the GraphPad Prism 7.0 software package (GraphPad Software, San Diego, CA, USA).

3. Results and discussion

Age at diagnosis is a well-known predictive factor in the most varied types of cancer, especially in leukemias. Patients whose age is less than one year or older than ten years are known to have worse outcomes in B-ALL (Rose-Inman and Kuehl, 2017; Wanitpongpun et al., 2021; Brown et al., 2021). In our group, as expected, the mean age at diagnosis was
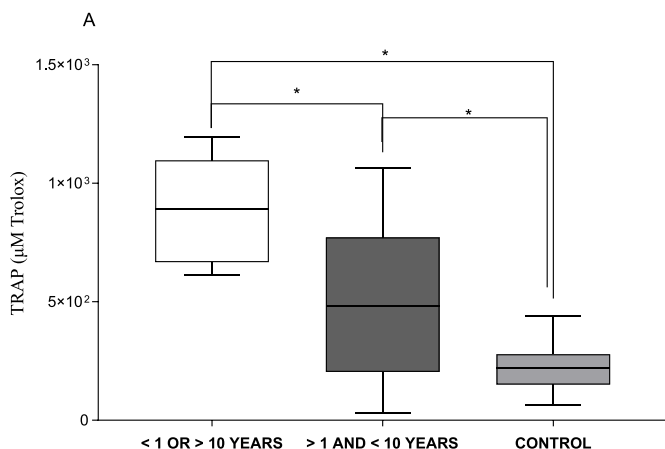
Fig. 2. Plasma antioxidant levels in pediatric patients with B-ALL according to age at diagnosis. Patients were categorized as older than 10 years at diagnosis or younger than 10 years. Control group included patients from all ages, ranging from 1 to 18 years. The data are represented in box plots (min-max). * indicates statistical significance (p < 0.05). TRAP = Total Plasma Antioxidant Capacity; Trolox = hydrosoluble tocopherol.

Table 1

Clinicopathological data and peripheral blood analysis of patients with B-ALL in the induction phase.

	B-LLA Patients
Total of patients	n = 34
Gender	
Female	n = 20 (58,82%)
Male	n = 14 (41,17%)
High Risk (D0)	n = 9
Deaths	n = 7 (77,7%)
Low Risk (D0)	n = 25
Deaths	n = 5 (20%)
Age at diagnosis, years (minimum-maximum)	7,4 (1,7–17,5)#
Leukometry/WBC, Peripheral Blood, mm3	
D0	17391 (400–75000)!
D28, induction	4393 (100–22400)!
Hemoglobin, g/dL	
D0	6,8 (2,9–9,3)^
D28, induction	8,8 (6,2–11)^
Peripheral Blood Antioxidants Analysis	
TRAP, μM of Trolox	
D0	577,40 (28,68–1194,71) *$&#
D7	343,25 (77,83–1223,07)*
D14	352,64 (53,43–777,1)$
D21	432,05 (52,27–960,02)&
D28	513,22 (89,03–1234,04)

Results are presented as median (min-max). TRAP (Total Antioxidant Capacity); μM (micromolar); Trolox (Vitamin E/Tocopherol); dL (Deciliter). Symbols indicate p < 0.05: # for Age at diagnosis vs TRAP D0; for leukometry on D0 vs D28; + for leukometry of patients who died vs. living patients; ● for TRAP deaths vs TRAP alive; ^ for hemoglobin on D0 vs D28; * for TRAP D0 vs D7; $ for TRAP D0 vs D14; & for TRAP D0 vs D21.

7.4 years. Considering that the daily diet directly influences the antioxidant capacity, body mass index, serum concentrations of copper-zinc, among other substances, and, mainly, by age, older individuals tend to have higher serum levels of antioxidants (Galan et al., 2005; Akhgarjand et al., 2018). Our result suggested that possibly due to leukemia, this antioxidant concentration could be a tumor defense mechanism that predicts poor prognosis seen in a large amount of TRAP in patients >10 years old when compared to children in this age group and the control group (Fig. 2).

The diagnosis of B-ALL is established by 20% or more lymphoblasts in the bone marrow, and the evaluation of cell morphology, flow
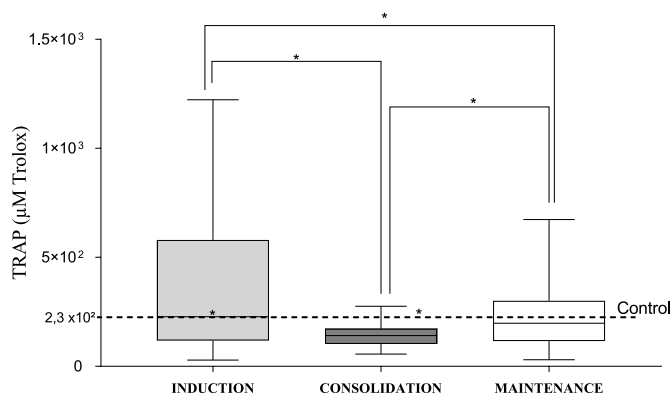

Fig. 3. Levels of antioxidants present in the plasma of pediatric patients with B-ALL during the chemotherapy treatment phases compared to the control group. The data are represented in box plots (min-max). * indicates statistical significance (p < 0.05). TRAP = Total Plasma Antioxidant Capacity; Trolox = hydrosoluble tocopherol.

cytometry, immunophenotyping, and cytogenetic tests are essential in risk stratification and diagnosis (Terwilliger and Abdul-Hay, 2017; Luca, 2021). Other tests include complete peripheral blood white cell count and clotting profile. In our study, the mean white cell count decreased during the induction phase (Table 1; p = 0.0159), while hemoglobin had a mean recovery of 2 g/dL at the end of D28 (Table 1; p = 0.0325). It suggests eliminating leukemic cells and bone marrow recovery due to pro-oxidant chemotherapy and improved nutritional support offered in a hospital environment.

The increase in oxidative stress markers in the plasma of B-ALL patients is accompanied by an increase in the synthesis of antioxidant enzymes that promote the survival of leukemic blasts in a pro-oxidant environment promoted by conventional chemotherapy. These enzymes have been studied as targeted therapy, such as in the thioredoxin and glutathione (GSH) system (Probst et al., 2017; Fidyt et al., 2019; Chen et al., 2021). In this sense, in our study, peripheral blood analyses revealed that patients on day 0 of treatment (D0; 28.68–1194.71 μM Trolox) had higher levels of antioxidants compared to D7 (70.84–1223.07 μM Trolox), D14 (53.43–744.75 μM Trolox) and D21 (52.27–960.02 μM Trolox) with p-values 0.0178, 0.0377 and 0.0392, respectively (Table 1). Thus, the drop in antioxidant levels in these patients is, in part, related to the large amount of cytotoxic and pro-oxidant drugs used in the induction phase. This reduction is possibly essential for complete remission of B-ALL to occur.

Oxidative stress is a complex result of the imbalance generated by chemical reactions and immune responses by pro-oxidant substances (such as LOOH and NOx) and antioxidants (such as TRAP) (Broto et al., 2021; Hooke et al., 2020). Low levels of oxidative stress in the microenvironment are necessary for correct bone marrow functioning. Therefore, increased reactive oxygen species (ROS) can lead to failed hematopoiesis and tumorigenesis. Glutathione S-transferase (GST) polymorphisms increase the risk of relapse in ALL (Hole et al., 2011; Leonardi et al., 2017; Dong et al., 2021; Di Martino et al., 2021; Chen et al., 2021).

One month of induction can eliminate approximately 99% of leukemic blasts, reaching complete remission in up to 90% of children. In this sense, the responsiveness to these drugs in the first phase will determine the long-term prognosis of B-ALL (Broto et al., 2021). Thus, the characterization of oxidative stress parameters at diagnosis (D0) and the following treatment phases can help understand how oxidative stress mediators behave during treatment and how the disease responds in each phase, intending to improve risk stratification protocols and reduce the number of relapses and deaths.

In this sense, the comparison of TRAP between the three treatment phases revealed a considerable reduction in consolidation
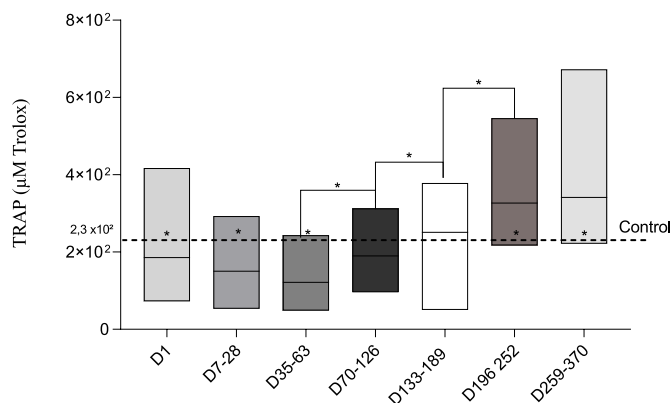
Fig. 4. Antioxidant profile behavior of B-ALL patients during maintenance treatment. The data are represented in box plots (min-max). * indicates statistical significance (p < 0.05). Legend: TRAP = Total Plasma Antioxidant Capacity; Trolox = hydrosoluble tocopherol.

(56.14–352.05 μM Trolox) when compared to Induction (28.68–1390.26 μM Trolox) and the control group (64.82–437.82 μM Trolox) and later increase in maintenance (30.48–672.99 μM Trolox) (Fig. 3; Induction vs. Consolidation p=<0.0001; Consolidation vs. Control Group p < 0.0001; Consolidation vs. Maintenance p = 0.0025). Considering the intensity of chemotherapy applied during the induction phase (Fig. 1), it is understandable that there is a global decrease in antioxidant status, with the suppression of bone marrow and consequent destruction of leukemic blasts. Also, an improvement was observed in the maintenance phase due to reduced chemotherapy and bone marrow recovery. The levels of antioxidants in the induction phase were slightly higher than in the maintenance and control group (Fig. 3; Induction vs. Maintenance p < 0.0001; Induction vs. Control p < 0.0001). It shows that in patients at the beginning of treatment, the redox balance is biased towards antioxidants; therefore, this increase may be a mechanism that favors chemoresistance and, consequently, worse outcomes. Thus, more effective pro-oxidant therapies should be investigated since traditional ROS inducers are often ineffective in eradicating residual disease (Burt et al., 2019; Dong et al., 2021).

Antioxidant enzymes such as catalase (CAT) and superoxide dismutase (SOD) are reported as mechanisms to escape chemotherapy in ALL (Battisti et al., 2008; Iyappan et al., 2021; Chen et al., 2021). It is reinforced by the fact that the inhibition of SOD by anticancer agents has a beneficial effect, resulting from the induction of apoptosis of leukemic cells through a mechanism mediated by free radicals (Zhou et al., 2003; Chen et al., 2021).
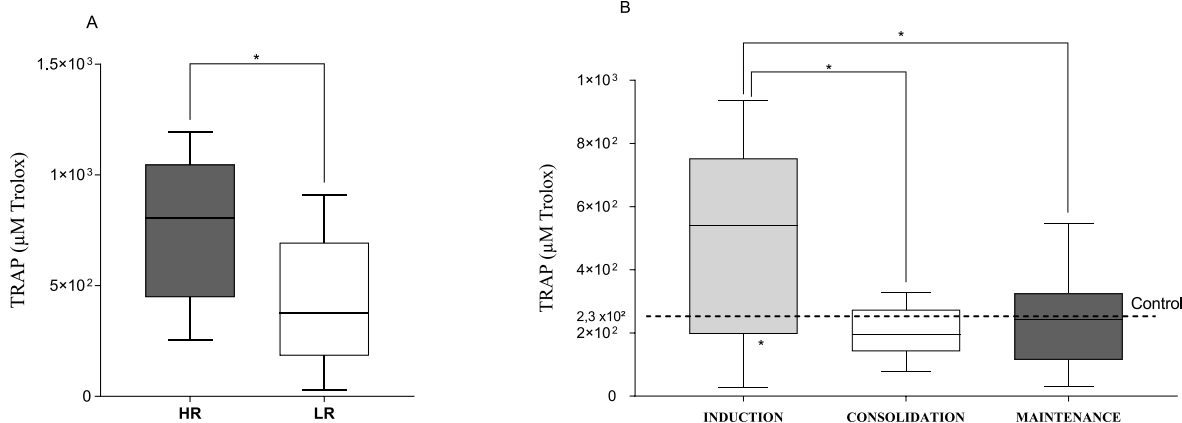
Despite the application of intrathecal medications in the consolidation phase (Fig. 1), there were no significant variations in the levels of antioxidants. However, when analyzing the profile of patients during maintenance, a considerable increase in antioxidants was observed, especially at the end of this phase, and at the end of maintenance, levels reached the same levels as healthy and disease-free patients belonging to the control group (Fig. 4; D35-63 VS D70–126 p = 0.0367; D70-126 VS D133–189 p = 0.0270; D133-189 VS D196–252 p = 0.0401). This normalization of the antioxidant profile demonstrates bone marrow recovery after the stress generated by cytotoxic therapy and consequent disease remission.

Before chemotherapy treatment, patients are classified into high and low risk at diagnosis according to some clinical laboratory parameters. The most relevant is the white blood cell count and age. Both parameters are predictive factors of response established in the literature, with those at high risk having a white cell count >50,000 cells/mm^{3} and/or age at diagnosis <1 or >10 years (Rose-Inman and Kuehl, 2017; Brown et al., 2021).

It was observed that patients at low risk (LR) had reduced levels of antioxidants compared to those at high risk (HR) (Fig. 5A; p = 0.0314). Also, there was a considerable reduction during treatment if comparing the values of the control group at the end of maintenance (LR Induction vs. LR Consolidation p = 0.0332; LR Induction vs. Consolidation Fig. 5B; p = 0.0032). The high TRAP with the HR group reveals that antioxidant levels are related to more significant disease severity/advancement. However, it must consider that the time of evolution of the disease until the moment of diagnosis can influence these levels, and, therefore, more studies in the area are still necessary. Finally, the gradual reduction of TRAP in the LR group had the same behavior as the study as a whole, reinforcing that the natural behavior of B-ALL in the face of the cytotoxic treatment of the GBTLI protocol is the gradual reduction of antioxidants, and those that have this drop have better clinical outcomes and longer disease-free time. This study has some limitations, including the small number of patients and the lack of analysis of the antioxidant profile at more blood collection points throughout the treatment. But despite that, as far as is known, this is the first study that addresses this issue. Our patients arrived on D0 without previous chemotherapy, and it was possible to identify phenomena not previously described. Thus, additional studies are needed to understand these findings better.

4. Conclusions

Our results indicate that the total antioxidant capacity varies according to the chemotherapy treatment in pediatric patients with B-ALL, being higher at diagnosis and lower at the end of treatment, suggesting that this increase may be a tumor defense mechanism of leukemia. In

Fig. 5. A - Antioxidant profile behavior of patients classified as Low Risk (LR) compared to those classified as High Risk (HR) at diagnosis. B – Variation of antioxidants during the chemotherapy treatment phases of the Low Risk group compared to the control group. The data are represented in box plots (min-max). * indicates statistical significance (p < 0.05). Caption: LR = Low Risk; HR = High Risk; TRAP = Total Plasma Antioxidant Capacity; Trolox = hydrosoluble tocopherol.

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addition, patients whose antioxidant profile is high and those aged over ten years and/or with a white blood cell count >50,000 cells/mm^3 at diagnosis tend not to respond adequately to chemotherapy and consequently have a worse prognosis. These findings may have future clinical implications, suggesting that quantification of antioxidants can be used at diagnosis and during treatment phases as a response predictor biomarker, helping to predict which patients will respond adequately to standard chemotherapy.

CRediT authorship contribution statement

Matheus Ricardo Garbim: Conceptualization, Methodology, Software, Data curation, Writing – review & editing, Writing – original draft, Preparation. **Geise Ellen Broto:** Conceptualization, Methodology, Software, Data curation, Writing – review & editing, Writing – original draft, Preparation. **Fausto Celso Trigo:** Conceptualization, Methodology, Software, Data curation, Writing – review & editing, Writing – original draft, Preparation. **Vanessa Jacob Victorino:** Conceptualization, Methodology, Software, Data curation, Writing – review & editing, Writing – original draft, Preparation. **Stefania Tagliari de Oliveira:** Conceptualization, Methodology, Software, Data curation, Writing – review & editing, Writing – original draft, Preparation. **Décio Sabbatini Barbosa:** Conceptualization, Methodology, Software, Data curation, Writing – review & editing, Writing – original draft, Preparation. **Carolina Panis:** Conceptualization, Methodology, Software, Data curation, Writing – review & editing, Writing – original draft, Preparation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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