Plan Overview

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Title: GLYCOCORTICOID SENSITIVITY AND ITS RELATIONSHIP TO COMPONENTS OF THE METABOLIC SYNDROME IN PATIENTS TREATED FOR CHILDHOOD ACUTE LYMPHOCYTIC LEUKEMIA

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Project abstract:

Acute lymphocytic leukemia (ALL) is the most prevalent cancer in childhood and glucocorticoid (GC) is an important drug in its treatment. The relationship between sensitivity to GC, response to treatment, determining toxicity and disease prognosis has already been studied and mechanisms that determine it have also been established (glucocorticoid receptor - GR isoforms and polymorphisms). However, the correlation between GC sensitivity and changes in its receptor with an unfavorable metabolic phenotype, determining obesity, insulin resistance (IR) and other components of the metabolic syndrome (MS) has not yet been established in this subgroup of patients. The objective is to determine, in patients treated for childhood ALL, the components of MS, including central obesity, lipids, blood pressure and glucose/insulin, to assess the sensitivity to GC, through sensitivity tests, polymorphic variants of GR and in vitro examinations (real-time quantitative polymerase chain reaction, qrt-PCR) and to correlate clinical and metabolic profiles with GC sensitivity. The proposal is to evaluate 30 patients treated for ALL in childhood, of both sexes, post-pubertal and for at least two years out of therapy, evaluated according to clinical characteristics, related to the disease and treatment, anthropometric variables (weight, height and body mass index), adiposity indexes (circumferences and their

relationships, fat mass by double-beam X-ray absorptiometry and abdominal fat by abdominal tomography), endocrine-metabolic profile (lipids and IR), GC sensitivity tests (0.25 mg overnight suppression test with oral dexamethasone and intravenous very low dose dexamethasone suppression test), determination of polymorphic variants of GR and quantification of mRNA of its processing variant GR-α by qrt-PCR. It is known that GC sensitivity, determined by the expression of mRNA of the different isoforms and/or the presence of specific polymorphisms in the GR, is one of the factors involved in the response to treatment and an important prognostic factor in ALL. The importance of this study is to understand the relationship between sensitivity to GC and unfavorable metabolic phenotypes in patients treated for ALL in childhood. The applicability of the results found here will be important to define a group of children and adolescents treated for ALL that deserves more attention during routine endocrine-metabolic screening and that, therefore, would have a higher risk for cardiovascular disease in adulthood.

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Study population

Patients diagnosed with childhood acute lymphocytic leukemia (ALL) followed at the Hospital of the Support Group for Children and Adolescents with Cancer (GRAACC) of the Federal University of São Paulo - UNIFESP/EPM. The study design is a dynamic cohort with a historical component (collection of data from medical records). Patients to be studied: 30.

Inclusion criteria

Patients of both genders who meet the following inclusion criteria will participate in the study:

Complete clinical remission, defined as the absence of peripheral blood or bone marrow disease in response to treatment; Out of treatment for at least two years; Complete pubertal development, characterized by the presence of menarche in girls and Tanner IV or more in boys (chronological age > 18 years);
Growth velocity < 1.0 cm in the year preceding the study and bone maturation with complete epiphyseal fusion; Normal thyroid and gonadal function, either spontaneously or under specific hormone replacement.

Exclusion criteria

Current use of anorexigenic or satietogenic drugs, insulin sensitizers, glucocorticoids, or other medication that may interfere with adiposity or metabolic profile; Use of exogenous growth hormone (GH) less than two years before the date of inclusion in the study; Down syndrome or hematopoietic stem cell transplant recipient (HSCT); Current pregnancy or delivery less than 90 days from the date of study inclusion.

Recruitment

Patients being followed at GRAACC will be recruited during consultations at the Pediatric Endocrinology Unit, Leukemia Out of Therapy and CFort (Out of Treatment Clinic) outpatient clinics or by active search via telephone.

Procedures

For each patient, a form will be filled out with anthropometric and clinical data obtained from medical records, clinical and physical examination.

Patients will be evaluated according to clinical characteristics, related to the disease and treatment (data from medical records), anthropometric variables (weight, height and body mass index - BMI), adiposity indexes (circumferences and their relationships, fat mass by dual-energy X-ray absorptiometry and abdominal fat by computed tomography), endocrine-metabolic profile (lipids and insulin resistance - IR), glucocorticoid (GC) sensitivity tests (suppression test with oral dexamethasone - TSD 0.25 mg overnight, and intravenous suppression test with very low dose of dexamethasone - VLD-IV-DST), determination of polymorphic variants of glucocorticoid receptor (GR) and quantification of mRNA of its processing variant GR-α by quantitative real time PCR (qrt-PCR).

Statistical analyses

Statistical analyses will be performed using IBM SPSS software for Windows (SPSS, Inc, Chicago, IL). For

categorical variables, results will be expressed in number and frequency; and for the numerical ones, in mean, median, standard deviation, minimum and maximum.

The sensitivity to GC of patients treated for childhood ALL will be compared to normal values already established in the VLD-IV-DST (Faria et al., 2008) by means of t tests for independent samples. Patients will be divided regarding the response to GC sensitivity tests, levels of GR-α mRNA and different polymorphic variants of GR (Bc1I-NR3C1 and A3669G), and compared according to clinical characteristics, those related to the disease and treatment, adiposity indexes, and metabolic syndrome (MS) traits using t tests for independent samples or analysis of variance (ANOVA). The relation between patient characteristics, those related to disease and treatment, adiposity indexes and the components of the MS with the response to GC sensitivity tests, the presence of certain polymorphic variants of GR and the levels of GR-α mRNA will be performed using correlation tests, and/or regression analysis. In all tests, 0.05 or 5% will be set as the level of significance.

Data will be entered in Excel spreadsheets, in specific tabs for each analysis performed, to enable further statistical analysis in a specific program (SPSS Statistics).

The study was approved by the Ethics Committee of UNIFESP/EPM (number 0073/2018) and by the Scientific Committee of GRAACC (IOP-046/2017).

Patients will be instructed about the research procedure and an Informed Consent Form will be signed.

Data are property of the Federal University of São Paulo - UNIFESP/EPM and may, however, be available in public banks after the publication of scientific articles in specialized journals. Access to scientific articles will follow the criteria of the journal's access rules.

Data will be stored on the Google Drive cloud system and on the personal computers of the researchers involved, as well as copies of the contents will be stored on an external HD.

Access to the content will be carried out by the researchers involved in the project, using a password. Data may be available to anyone who has had a legitimate and proven interest and who requests access to them.

All data obtained will be stored for at least 10 years after the end of the study.

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Data will be shared through the publication of scientific articles and through the institutional repository of the Federal University of São Paulo - UNIFESP/EPM.

Data will be accessible to everyone who has a scientific interest and may generate new conclusions from them and will be shared after the publication of the work in scientific journals. However, it is possible that there may be some restriction on sharing data due to the gap imposed by the copyright of the scientific journals.

Researchers involved in the project will be responsible for the data (Beneficiary: Adriana Aparecida Siviero Miachon).

The resources needed consist of broad access to online platforms that allow access to the collection of documents and connection with interested parties.

Analysis of steroids by standardized techniques, in addition to the knowledge of Molecular Biology techniques for the analysis of polymorphic variants/isoforms of the glucocorticoid receptor (GR), and quantification of mRNA of GR-α by quantitative real time PCR (qrt-PCR).
