Research Article

Transforming Growth Factor Beta 1: Possible Involvement with Acute Lymphoblastic Leukemia Prognosis in Pediatric Patients

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ARTICLE INFO

Article history:
Received: 21 August, 2020
Accepted: 25 September, 2020
Published: 30 September, 2020

Keywords:
Acute lymphoid leukemia
TGFB1
polymorphism
treatment

ABSTRACT

Acute lymphoblastic leukemia (ALL) is a malignant hematologic disorder and the most common cancer in children. Polymorphisms of TGFB1 gene have been associated to TGFB1 altered expression, disease susceptibility and prognosis. The present study evaluated polymorphisms of the TGFB1 promoter region and plasma levels of TGFB1 in 104 ALL patients and 115 controls. Furthermore, it was investigated its possible involvement in different clinical stages of ALL. Both polymorphisms were not associated with ALL susceptibility or risk of relapse and their different genotypes did not alter TGFB1 plasma levels. However, it was verified decreased of TGFB1 concentration in ALL compared to control group (p<0.0001). TGFB1 plasma levels were significantly lower in ALL patients at diagnosis comparing to treatment (p=0.004) and remission (p<0.0001) groups. Notably, patients in remission presented similar TGFB1 plasma levels to controls. This work demonstrated the effects of a deregulated immune function in childhood ALL concerning to TGFB1 regarding prognosis and suggests TGFB1 recovery induced by treatment.

Introduction

Acute lymphoblastic leukemia (ALL) is a malignant hematologic disorder and the most common cancer in children up to 2 and under 5 years old, occurring less frequently in adults. It occurs in adulthood less frequently. Although the etiology remains unknown, it has been revealed that exogenous and endogenous exposures might result in ALL’s pathogenesis [1]. In Brazil, the National Cancer Institute has estimated 10,810 new cases of leukemia in 2020, with the highest incidence in childhood [2]. Chemotherapy constitutes the basis for ALL treatment; however, it negatively influences immune system, potentially allowing life threatening opportunistic infections. In fact, immunological impairment persists in leukemia patients for the whole treatment period and after its completion [3]. In this setting, the relation between immune system and tumor immunity has becoming a relevant issue due to the fact that cells and cytokines secretion are involved in modulation of tumor microenvironment [4, 5].

The transforming growth factor beta (TGFB) family constitutes a multifunctional set of cytokines that regulate a bewildering array of cellular processes during development and beyond. In this regard, TGFB1 is considered a multi-faceted cytokine with opposite functions at the initial and late stages of cancer. Furthermore, this cytokine has demonstrated many functions, including immunoregulation, regulation of tumor microenvironment and modulation of hematopoietic system-bone marrow axis [6-8]. The TGFB signaling pathway plays a fundamental role in several cellular processes and mutations in the genes of this pathway are involved in hematological diseases [9-12].

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http://dx.doi.org/10.31487j.COR.2020.09.11
It is known that genetic polymorphisms or sequence variants are commonly distributed throughout human genome and may be associated with disease susceptibility and/or prognosis. On the basis of this assumption, the functional impact of a polymorphism can alter gene function, and could predict the likelihood of association of a given condition [13]. It has been reported that TGFβ1 variants have subtype-specific roles in breast cancer and may switch from tumor suppressor to promoter during tumor development [14]. Polymorphisms in the promoter region of TGFβ1 gene have been associated to TGFβ impaired expression [15]. Two of them, rs1800468 and rs1800469, located at -800 and -509 positions from start codon, result in G>A and C>T mutation, respectively. However, their effects on the role of TGFβ1 gene remains unclear.

In this study, we performed a case-control study by analyzing polymorphisms in the TGFβ1 promoter region (rs1800468 and rs1800469) and determined TGFβ1 plasma levels to evaluate a possible functional correlation among the two polymorphisms and protein levels. Moreover, we investigated its possible involvement with ALL prognosis.

Materials and Methods

I Study Population

The protocol was approved by the Ethics Committee for Research Involving Human Subjects of Londrina State University (CEPUEL 189/2013—CAAE 17123113400005231) and all study subjects (children's parents) signed a free informed consent form prior to biological material collection. The diagnosis of ALL was classified according to the European Group for Immunophenotyping of Leukemias (EGIL) recommendations [16]. Philadelphia chromosome status was assessed by cytogenetic analysis and by molecular methods, when applicable. All patients included in the trials before January 2018 who achieved complete remission and for whom there was at least 3 years of follow-up after obtaining the complete remission were reviewed. Patients identified as having relapsed were selected and critical data (date of relapse, date of second remission if attained, date of subsequent relapse, survival status, date of last contact or death and cause of death) were obtained for all patients.

Blood samples (5 mL) were obtained from 104 ALL pediatric patients (52 males and 52 females) (mean age 8.6 years) with clinical and pathological data available from the Londrina Cancer Hospital. For the control group, blood samples of 115 children (53 males and 62 females) (mean age 10.9) without cancer or inflammatory diseases (based on hematological, biochemical and serological tests) were collected at Clinical Hospital from Londrina State University (HC-UEL).

Table 1: Allele and genotype frequencies of the rs1800468 and rs1800469 polymorphisms in ALL patients and controls.

| SNPs   | Allele/ Genotype | ALL N (%) | Control N (%) | OR (CI 95%) | p value* |
|--------|------------------|-----------|----------------|-------------|----------|
| Allele frequency |                   |           |                |             |          |
| rs1800468 | G                | 198 (95.19) | 219 (4.78)     | 1.01 (0.42-2.42) | 1.00     |
|          | A                | 10 (4.81)  | 11 (95.22)     |             |          |
| rs1800469 | C                | 81 (38.94) | 145 (63.0)     | 1.11 (0.75-1.63) | 0.62     |
|          | T                | 127 (61.06)| 85 (37.0)      |             |          |
| Genotypes | rs1800468       | GG        | 94 (90.38)     | 106 (92.17)  |          |

II Genomic DNA Extraction

DNA was extracted from peripheral blood cells using Biopur Mini Spin kit (Biometrix Diagnóstica®, Curitiba, Paraná, Brazil) and quantified in a NanoDrop 2000c Spectrophotometer (ThermoFisher Scientific, Wilmington, DE, EUA). The restriction fragments were analysed by electrophoresis on polyacrylamide gel (10%) stained with silver nitrate.

III TGFβ1 Genotyping

Genetic polymorphisms were analysed by Polymerase Chain Reaction (PCR) followed by Restriction Fragment Length Polymorphism (RFLP) analysis, according to previous studies [14, 17]. All PCR reagents were purchased from Invitrogen™ (Carlsbad, CA, USA). To validate the primers specificity, PCR product sample was sequenced in a Sanger-based platform (Applied Biosystems® 3500 Genetic Analyzer). All restriction enzymes were from New England Biolabs® (Ipswich, USA). The restriction fragments were analysed by electrophoresis on polyacrylamide gel (10%) stained with silver nitrate.

IV Plasma TGFβ1 Quantification

Peripheral blood TGFβ1 was quantified using BD OptEIA™ Human TGFβ1 Set (BD Biosciences Pharmingen, San Diego, USA). Briefly, blood plasma from each group was added into the precoated plate with monoclonal anti-human TGFβ1. The results were expressed in ng/ml. Each experimental and control sample was assayed in two biological replicates. Data was performed using the analytical curve-fitting software Gen5 (BioTek, Instrument Corporation, VT, EUA).

V Statistical Analysis

Chi-square test was used to Hardy-Weinberg equilibrium analyze. Case control association study was performed using contingency tables to calculate the Odds Ratio (OR), with 95% confidence interval (CI), and Fisher exact tests. Cytokine levels were analysed using non-parametric Mann-Whitney U test. All statistical analyses were performed by Prism 6 (GraphPad Software, San Diego, USA) and significance level set at 0.05.
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Clinical Oncology & Research
doi:10.31487/j.COR.2020.09.11
Volume 3(9): 3-6

Results

Risk of relapse was determined by protocol prescribed by the Brazilian Cooperative Group for the Treatment of Childhood Leukemia (GBTLI) and the ALL classification included age and leukocyte count at diagnosis, immunophenotyping, involvement of central nervous system and treatment responsiveness [18]. In this context, 33 patients were classified as low-risk and 71 as high-risk patients. The patients and controls were predominantly Caucasian, a prevalent population in southern Brazil due to European colonization.

Table 2: Risk association between TGFB1 rs1800468 and rs1800469 genotypes and ALL risk of relapse.

| Genotypes | OR (CI 95%) | p value |
|-----------|------------|---------|
| rs1800468 |            |         |
| AA+GA    | N (%)      | N (%)   | 1.55 (0.40-5.92) | 0.47 |
| GG       |            |         |
| Low risk | 4 (3.85)   | 28 (26.92) |
| High risk| 6 (5.77)   | 65 (62.5)  |
| rs1800469 |            |         |
| TT+CT    | N (%)      | N (%)   | 1.26 (0.51-2.90) | 0.66 |
| CC       |            |         |
| Low risk | 21 (20.19) | 11 (10.58) |
| High risk| 44 (42.30) | 28 (26.92) |

Figure 1: TGFB1 plasma levels. The results were expressed in ng/ml for TGFB1. Each sample including controls (CC) and ALL patients was assayed in two biological replicates. S.E.M. as error bars.

Figure 2 shows plasma levels from ALL patients based on therapeutic regimen: twenty-five patients were at diagnosis, who have not yet received any therapy; 48 were undergoing treatment (Treatment group) and 17 of them were in complete remission but receiving low-dose maintenance chemotherapy (Remission group). Interestingly, in the analysis of chemotherapy effect, TGFB1 plasma levels were significantly lower in diagnosis (mean 2.78 ng/mL ± 0.89), comparing to treatment (8.52 ng/mL ± 1.77; p=0.004) and remission (14.81 ng/mL ± 2.86; p<0.0001) groups. Notwithstanding, plasma levels of TGFB1 in the Remission group were similar to control group (p=0.61). After treatment, the relapse group increased TGFB1 concentration (7.124 ng/mL ± 0.84). TGFB1 levels in ALL patients were compatible with the
relapse and the moment of diagnosis, that is, a patient not yet submitted to chemotherapeutic treatment.

![Figure 2: TGFβ1 plasma levels in control and ALL patients according therapeutic modality. Patients were grouped for diagnosis, treatment phase, remission, relapse and after treatment. S.E.M. as error bars.](image)

**Discussion**

This study demonstrates the involvement of TGFβ1 plasma levels in the prognosis of ALL, and suggests recovery of TGFβ1 induced by ALL treatment. TGFβ1 is considered as pleiotropic cytokine, regulating cell cycle, differentiation, proliferation, recognition and apoptosis in virtually all tissues of the body, including hematopoietic [19–21]. Particularly in the last, TGFβ1 controls quiescence and self-renewal of hematopoietic stem cells, processes that are disrupted in leukemic cells [8]. Regardless of its multifunctional feature, genetic polymorphisms could interfere in TGFβ1 expression, thus, affecting its downstream signaling pathways. Therefore, the rs1800468 and rs1800469 polymorphisms in the promoter region TGFβ1 in ALL patients were under investigation.

To date, there are few studies comparing these polymorphisms in ALL patients. Dai, Gast have demonstrated no associations of genotypes and allelic frequencies of TGFβ1 and TGFβ2 polymorphisms in German ALL patients [22]. Likewise, Healy, Roy-Gagnon reported no significant association of rs1800469 TGFβ1 polymorphism in French Canadian pre-B ALL patients [23]. In this context, we did not find significant differences in genotype distribution and allelic frequencies of promoter region TGFβ1 polymorphisms rs1800468 and rs1800469 among ALL patients and controls. Furthermore, neither allelic nor genotypic frequencies were associated to ALL risk of relapse. Thus, it is reasonable to assume that such polymorphisms in TGFβ1 promoter region may not represent good predictive biomarkers of ALL susceptibility or recurrence.

On the other hand, the impact of these gene polymorphisms in TGFβ1 expression have been questioned. The rs1800469 polymorphism is located in a consensus sequence of TGFβ1 promoter recognized by Yin Yang 1 (YY1) transcription factor, and the substitution of cytosine (C) to thymine (T) increases the YY1 affinity to the site, increasing cytokine circulating concentration [24]. Contrariwise, the rs1800468 polymorphism is positioned in a putative site for cAMP-response element binding factor (CREB) family of transcription activators, and the A allele may decrease CREB members affinity to the site [25].

In the present study, TGFβ1 was quantified in plasma of ALL patients and controls for comparing the effect of different genotypes of rs1800468 and rs1800469 polymorphisms in cytokine concentration, however, there were no differences in plasma TGFβ1 concentration regarding the genotypes of these polymorphisms. Considering data dispersion of TGFβ1 plasma levels in both groups, therefore, it is unclear whether these polymorphisms have actually functional roles in TGFβ1 plasma expression, and it is difficult to draw any meaningful conclusion. Interestingly, ALL patients presented significantly lower TGFβ1 plasma levels in comparison to controls. These results are in accordance to the findings of Chen, Lu, who shown that serum TGFβ1 levels were significantly decreased in acute leukemia patients, restored to normal in patients who achieved complete remission, and tended to decrease again in patients who develop recurrence [26]. Conversely to our results, Al-Mowallad, Carr demonstrated that no significant difference in TGFβ1 plasma levels was shown between 60 children with ALL at diagnosis and controls [27].

The cytokine system constitutes a functional network in physiological and pathological conditions, and alterations in this setting may affect direct or indirectly leukemogenesis through altered functions of bone marrow stromal elements [28]. In this context, TGFβ is an essential regulator of cellular processes, including proliferation, differentiation, migration and cell survival, and is perhaps the most potent endogenous negative regulator of hematopoiesis [29, 30].

It is known that tumor cells are often resistant to signals that inhibit growth of their normal cell counterparts. Escape from such control mechanisms may contribute to malignant transformation [31]. Thus, we suggest that downregulation of TGFβ1 expression observed in plasma from ALL patients might result in unlimited proliferation of malignant cells, which in turn may contribute to the bone marrow hyperplasia and peripheral blood invasion of leukemic clones. In order to demonstrate the role of chemotherapy in TGFβ1 plasma levels, samples were grouped according to therapeutic regimen at the time of sampling and the analysis revealed important differences, in the main, a reestablishment of TGFβ1 plasma levels in ALL patients during treatment. As a hematological malignancy, basic therapeutic agents used in the treatment of ALL are cytotoxic drugs with exert immunosuppressive effects, which requires monitoring of the immune system following cessation of therapy [32].

Indeed, our results demonstrated lower TGFβ1 levels in patients before chemotherapy compared to treatment and remission group. Nevertheless, plasma concentration of TGFβ1 during remission was comparable to controls. This variation may reflect the immune status of the patient, the chemotherapy response and/or the TGFβ1 gene regulation per se. The SKI gene encodes the nuclear protooncogene protein homolog of avian sarcoma viral oncogene, and is expressed in both T and B mature murine hematopoietic lineage cells [33, 34]. One of its function is to interact with SMADs proteins family and represses the ability of the SMADs to mediate TGFβ-induced growth arrest and transcriptional activation [35].

*Clinical Oncology & Research* doi:10.31487/j.COR.2020.09.11 Volume 3(9): 4-6
Moreover, the oncoprotein EVII has been shown to bind with SMAD3 and inhibit the activation of TGFβ responsive promoters by disrupting the binding of Smad3-Smad4 complex to DNA [36]. TG-interacting factor (TGFIF) is another oncoprotein that can interact with TGFβ-activated SMADs and represses expression of TGFβ target genes [37]. These studies establish roles for the TGF-β signaling pathway in aspects of the pathogenesis of hematologic malignancies, major challenges in the TGFβ1 signaling field remain in defining specific pathways involved in mediating the cell- and context-dependent effects of TGFβ1 [29]. Altogether, despite the fact that none of these negative TGFβ regulators were investigated in this study, our results strengthened the hypothesis that downstream effects of TGFβ signaling cascade are altered in ALL, since TGFβ1 plasma levels are decreased at diagnosis and at relapse.

In summary, our study evidenced the effects of a deregulated immune function in childhood ALL concerning to TGFβ1 when predicting prognosis. It is not known exactly which gene or protein are repressing TGFβ1 production in ALL at diagnosis. Nonetheless, further molecular and functional investigations are necessary to determine whether the association of TGFβ1 plasma levels may also be influenced by other polymorphisms in its gene and structural haplotypes. Finally, in addition to the potential molecular influence of TGFβ1 repressors, the results of this study may also indicate a significant impact of chemotherapy on TGFβ1 levels. This could be of particular relevance in leukemia pathophysiology, highlighting the importance of evaluating the molecular mechanisms of certain drugs at restoring TGFβ1 levels during ALL patients’ treatment.

Conflicts of Interest

None.

Acknowledgments

The authors would like to thank Londrina Cancer Hospital, Parana, Brazil, Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Fundação Araucária do Paraná, Secretaria da Ciência, Tecnologia e Ensino Superior (SETI), Fundo Estadual para a Infância e Adolescência (FIA/PR), Secretaria da Família e Desenvolvimento Social (SEDS) and Pro-reitoria de Pós-Graduação da Universidade Estadual de Londrina (PROPPG-UEL).

Funding

None.

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